Chapter 16
Osteoporosis and the Ageing Skeleton

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Abstract Osteoporosis is a "skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture" which, in light of demographic change, is becoming an increasing burden on health care worldwide. Increasing age and female gender are associated with the condition, although a wider range of clinical risk factors are being used increasingly to identify those at risk of osteoporosis and its most important sequelae, fracture.

While osteoporosis and fracture have long been associated with women in the post-menopausal age, fracture incidence increases because of the ageing of our population. Interventions to abate the progression of osteoporosis and to prevent fractures must focus on the old and the very old. Evidence associating nutritional factors, particularly calcium and vitamin D are reviewed as are the association of falls risk with fracture and the potential for interventions to prevent falls. Finally, the assessment of frailty in the oldest old, associated sarcopenia and multi-morbidity are considered in the evaluation of fall and fracture risk and the management of osteoporosis in the ninth decade of life and beyond.

Keywords Osteoporosis · Bone mineral density · Hip fracture · Fracture risk assessment · Frailty · Calcium nutrition · Vitamin D · Sarcopenia · Frailty

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Introduction

Osteoporosis is a "skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture" (NIH 2001). In this clinical definition, we encounter two key themes. Firstly, the *quality* of the bone is affected and its strength weakened but secondly, and most important in a clinical context, the individual with osteoporosis is at increased risk of fracture. Some of the qualitative features may be observed in skeletal histomorphometry, with osteoporotic bone showing evidence of fewer trabeculae, an overall reduction in trabecular bone volume (see Fig. 16.1) and significant differences in microstructure when compared with normal controls. Differences in bone remodelling (bone turnover) may also be observed, with affected individuals having a low, normal or increased bone turnover, depending on the aetiology of osteoporosis (Steiniche 1995).

Unfortunately, bone histomorphometry is an invasive method of assessment and, although a gold standard diagnostic test for osteoporosis, other non-invasive ways of evaluating the strength of bone are required in practice. Estimates of mineral content by bone mineral density (BMD) correspond to bone strength in vitro (Rudang et al. 2016). Using this method, a beam of x-rays is passed through a skeletal site prone to fracture (spine, hip or wrist) and the attenuation of the x-ray beam is measured using x-rays of differing energies in a dual energy x-ray absorptiometer (DXA), with calibration of the measurement against a bone/soft tissue *phantom* (see Fig. 16.2). In a meta-analysis of prospective studies, BMD at either the spine or hip predict overall fracture risk, with a reduction in BMD by one standard deviation associated with a relative fracture risk of 1.5. Spinal fracture risk was better estimated where the measurement was made at spine with a relative fracture risk of 2.3 and similar findings were seen for hip measurements, predicting hip fracture with a relative risk of 2.6, which are in accordance with results of case-control studies

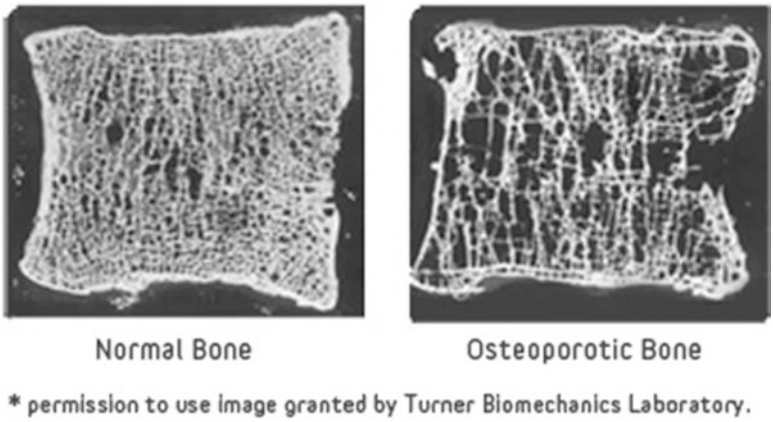

Fig. 16.1 Two slides comparing the vertebrae of a healthy 37 year old male with a 75 year old female suffering from osteoporosis. (Creative commons licence)

Fig. 16.2 A dual-energy X-ray absorptiometry (DXA) scan being administered. A man lies on the scanner while the arm of the scanner moves over him, taking a full scan of his body tissue density. (Creative commons licence)

(Marshall et al. 1996). However, two individuals of a similar BMD may still have very different likelihoods of sustaining a fracture. This is evident if we consider the child who has not yet achieved peak bone mass and whose BMD is similar to her grandmother, whilst she is at a much lower fracture risk. In vitro studies evaluate a number of parameters to assess bone strength, including elastic modulus, yield stress, yield strain, ultimate stress, ultimate strain, strain energy density, as well as fracture load by fracture force, maximum viscous response, energy at fracture and time to fracture. Notable variations are seen in such studies in the correlation of these parameters to BMD between skeletal sites, trabecular and cortical bone and between the variables themselves at individual sites (Beason et al. 2003; Kemper et al. 2006; Njeh et al. 1997). BMD may also be low in mineralisation disorder, such as seen in nutritional osteomalacia (Bhambri et al. 2006).

There are also other functional concerns to be considered in assessing the contribution of bone quality to osteoporosis. For example, we see that bone stiffness and BMD contribute independently to bone strength (Njeh et al. 1997). Beyond BMD, there have been technical advances in determining bone micro-architecture, using high resolution (HR) computed tomography (CT) at various anatomical sites. This permits the evaluation of bone micro-architecture including trabeculation and the measurement of cancellous bone porosity, which may both contribute to bone

strength independent of BMD (Vilayphiou et al. 2016). Large scale clinical trials of alternative bone measurement methodologies such as HR peripheral quantitative CT(HRpQCT) are not available but they may prove to be promising tools for evaluating bone quality in a wider sense than just the areal mean BMD currently measured by DXA. To complement such radiological methods, biochemical tests of bone formation (osteoblast function) and resorption (osteoclast function) are used in clinical practice. It is important to appreciate that there are a number of factors influencing bone turnover markers. In childhood and young adult life, there is an *anabolic* balance reflecting increased bone formation (higher bone-specific alkaline phosphatase or P1NP) with a consolidation of bone turnover throughout adult life, and relatively balanced levels of P1NP and CTX (a marker of osteoclast function) up to middle age. In women, at the beginning of the sixth decade, there is a marked increase in both resorption (CTX) and formation (P1NP) but a relative *uncoupling*, such that the increase in resorption is greater, and results in a decrease in BMD. Increased bone turnover has been identified as a risk factor for osteoporotic fractures independent of BMD, although more recently an influential case control study analysis of the Women's Health Initiative (WHI) study found no evidence that bone turnover markers predicted hip fracture (Crandall et al. 2018). Thus, these biomarkers tend to increase with age, after peak bone mass has been achieved in the late third or early fourth decade of life but, unfortunately, they are not useful at an individual level for estimating fracture risk (Eastell et al. 2018; Gossiel et al. 2014).

Fracture Epidemiology

Throughout life, there are gender disparities in fracture risk. In childhood and younger adult life, fracture incidence in males is greater and peaks in the decade aged 15–24 years with a UK annual incidence approaching 200 per 10,000, whereas fewer than 40 per 10,000 women experience a fracture (Donaldson et al. 1990). However, around the age of 50 years, the baton is passed on to women, whose annual fracture incidence is greater than for men thereafter, exceeding 450 per 10,000 in those aged over 85 years, compared with a rate of approximately 350 per 10,000 in men of this age in the UK (Donaldson et al. 1990). A similar pattern has also been seen elsewhere in the UK (Johansen et al. 1997) and in Australia (Pasco et al. 2015). Osteoporosis is not believed to be a major contributor to fracture risk in childhood and younger adult life, as boys and young men have a higher fracture incidence despite a greater BMD than girls and young women, while typical 'osteoporotic' fractures are rare in either gender before the age of 50 years. However, past the age of 50 years, fractures of the distal forearm, rib, pelvis, humerus, femur and patella increase among women, and rib, pelvis and humerus among men, in addition to fractures of the hip and spine (Pasco et al. 2015). At the age of 50 years, the lifetime risk of having a low trauma (*osteoporotic*) fracture is 53% for women and 21%

for men (van Staa et al. 2001). In older adults, the considerable gender disparity in fracture incidence continues to increase. While low trauma fractures of the wrist, hip and spine steadily increase from the sixth decade onwards, annual hip fracture incidence in women aged over 85 years are around 4%, compared with a risk for men of the same age group of 2% (Johansen et al. 1997). Overall, there is a 10–15 year time lag in fracture risk between men and women, although older men remain at significant risk of osteoporotic fracture in their seventh decade and beyond.

Internationally, there are differences in fracture incidence with ethnic differences observed as well as secular changes in osteoporotic fracture rates. Clearly, some of the differences in osteoporosis and fracture risk relate to demography, as countries with fewer old people will experience fewer fractures. However, age-standardized incidence rates of hip fracture also vary between countries by more than 200-fold in women and 140-fold in men, with age-standardized rates highest in North America and Europe and lowest in Africa. It is anticipated that crude fracture rates will show the greatest proportional increase in Africa, where demographic transition and the anticipated increase in the older adult population at risk of fracture will be seen most. A decline over time in hip fracture rates has been seen in some countries of North America, Europe and Oceania, most notably seen in women. However, hip fracture rates continue to increase in Asia and Latin America. Indicators of health, education and socioeconomic status such as Gross National Income (GNI) per capita, Human Development Index and life expectancy at birth are correlated to hip fracture incidence rates in men and women, even after adjustment for age. This supports the hypothesis that a number of lifestyle factors contribute to osteoporosis and fracture risk in older age and offers the promise that modification of these factors may be a tool for decreasing fracture risk (Cauley et al. 2014; Kannus et al. 1996; Melton 1993).

Risk Factors for Osteoporosis

There are a number of risk factors for osteoporosis, which can be viewed across the life course. Some have already been discussed: BMD, bone turnover (Vilaca et al. 2017) and bone microarchitecture (Vilayphiou et al. 2016), together with skeletal geometry (Leslie et al. 2016) and muscle (Malkov et al. 2015). These effects are primarily on bone itself, mediated through pathophysiology or anatomical effects on bone structure and strength. While fracture risk is greatest in the ninth decade of life and beyond, some of these factors may be effected in younger adult life, childhood or even the uterus, where skeletal size and density increase from early embryogenesis through intrauterine growth to infancy. Genetic and epigenetic effects- at least on BMD, have been identified, including maternal body build, lifestyle and 25(OH)-vitamin D status. These factors might have important effects on developmental plasticity, as the osteoporotic phenotype may be viewed as a product of genotype and the prevailing environment at various stages in life (Holroyd et al. 2012). Specific gene loci are being sought to explore the potential for epigenetic

mechanisms to influence BMD (Curtis et al. 2017; Morris et al. 2017; Yu and Wang 2016) and early work has shown that circulating MicroRNAs (miRNAs) have been linked to fragility fracture risk, at least in postmenopausal women with type 2 diabetes mellitus (Heilmeier et al. 2016).

Fracture Risk Assessment

More conventional clinical risk factors have also been identified, which focus on fracture risk assessment rather than the diagnosis of low BMD. These have been reviewed and over recent years adopted in the UK (although not Scotland) by the National Institute for Health and Care Excellence (National Institute for Health and Care Excellence 2012). The guidelines prompt good practice in case finding, using clinical risk factors. They recommend fracture risk assessment using clinical risk factors in women aged 65 years and over and men of 75 years and over with assessment of fracture risk in women and men under these ages if they have a risk factor (see Table 16. 1) but not to routinely assess fracture risk in people under 50 years of age unless they have ***major*** risk factors (*see* Table 16. 1), as they are unlikely to be at high risk. One of the indications for fracture risk assessment is the presence of a potential cause of secondary osteoporosis. A (non-exhaustive) list of these diseases is presented in Table 16. 2.

When assessing fracture risk, either FRAX or QFracture can be used to calculate a 10 year predicted absolute fracture risk. However, routine measurement of BMD without prior BMD measurement or the risk assessment can be refined by adding in BMD. The QFracture tool is derived from routine GP data on more than two million adults aged 30–85 years (Hippisley-Cox and Coupland 2009). It incorporates many more risk factors than FRAX but cannot use BMD to contribute to fracture risk assessment, since this is not routinely recorded in UK general practice. Unfortunately,

Table 16.1 Clinical risk factors for women aged 65 years and over and men aged 75 years and over

Previous fragility fracture[a]
Oral or systemic glucocorticoids[a]
Untreated early menopause (or male hypogonadism)[a]
History of falls[b]
Family history of hip fracture[b]
Secondary osteoporosis[b]
Low BMI (<18.5 kg/m^2)[b]
Smoking[b]
Alcohol intake[b] Women: >14 units/week Men: 21 units units/week

[a]These are major risk factors which apply to all ages

[b]These risk factors DO NOT apply to patients aged less than 50 years

Table 16.2 Causes of secondary osteoporosis

Endocrine Early menopause Hyperthyroidism Hyperparathyroidism Hyperprolactinaemia Cushing's disease Diabetes mellitus
Gastrointestinal Coeliac disease Inflammatory bowel disease Malabsorption syndromes e.g. short bowel
Rheumatological Rheumatoid arthritis
Haematological Multiple myeloma Haemoglobinopathies Mastocytosis
Respiratory Cystic fibrosis Chronic obstructive lung disease
Metabolic Homocystinuria Chronic kidney disease
Immobility For example: neurological injury

there are no calibration studies comparing the performance of FRAX and QFracture in predicting fracture incidence. FRAX has been developed, refined and calibrated for a number of nations (Fraser et al. 2011) and there are also a number of other tools worldwide, which have been developed with local and specific populations in mind. These tools vary, with some intended to predict BMD alone, while others focus on specific populations, such as the Garvan tool for fracture risk assessment in older people. Generally, there seems to be little to commend complex tools which incorporate many variables and it remains disappointing that there is so little research comparing tools in their performance, as discussed elsewhere (Aspray 2015).

Osteoporosis in Old Age

Most of the discussion so far in this chapter has considered osteoporosis in its widest context and not focused on those who are at greatest risk: the old. As already highlighted, BMD progressively declines from the fourth decade. The risk of fracture increases progressively into the ninth decade and beyond. Risk factors for fracture include increasing age, female gender and secondary osteoporosis (see

Table 16.2). In addition, there are a number of factors which are of particular relevance to an older population.

Nutrition: Calcium and Vitamin D

Nutritional osteomalacia, and rickets, in children, are the diseases most closely linked to calcium, vitamin D and skeletal health, although the effect of calcium and vitamin D status on the aetiology and treatment of osteoporosis is often highlighted. Evidence in this area is contentious. In the UK, the national diet and nutrition survey (NDNS) found that just 10% of women and 4% of men aged 75 years or over were taking less than the lower reference nutrient intake (LRNI) for calcium, which is a better proportion than seen in children and adults aged 11–64 years (Roberts et al. 2018). However, cases of mineralisation disorder due to osteomalacia are associated with low circulating blood levels of 25(OH) vitamin D, presumably relating to poor intakes and lack of sun exposure. Looking at the population aged 75 years or older in the NDNS survey, only 28% of the recommended nutrient intake (RNI) for vitamin D was obtained from diet and this increased to an average of 53% of RNI, when nutritional supplement sources were included. In the same survey, 11% men and 15% women had a circulating 25(OH) vitamin D concentration less than 25 nmol/L (Roberts et al. 2018), which the UK scientific advisory committee in nutrition (SACN) has confirmed as the threshold for risk to musculoskeletal health (Scientific Advisory Committee on Nutrition 2016). The risks of vitamin D deficiency are discussed in more detail elsewhere (see chapter on "Vitamin D in Biomedical Sciences" volume). However, interest has continued in the role of calcium and vitamin D in osteoporosis and fracture prevention. Epidemiological data from NHANES in North America have shown that lower dietary calcium intakes are associated with lower BMD, although this relationship is only seen in the population with a circulating 25(OH) vitamin D level less than 50 nmol/L (Bischoff-Ferrari et al. 2009b). A Swedish study of 5022 women followed up for 19 years found a non-linear relationship between fracture risk and calcium intake (including supplement). With the third quintile as reference (3.1 first hip fractures per 1000 person-years), the first hip fracture rates highest in the first quintile were 48% greater and the fifth quintile were 13% greater and similar relationships were seen for any fracture, any first fracture and any hip fracture (Warensjo et al. 2011).

Considering evidence from supplementation studies, one randomised controlled trial of calcium supplement in 1471 postmenopausal women showed a significantly higher BMD at the spine and the hip but no difference in fracture risk over 5 years (Reid et al. 2006), whereas the UK RECORD study, which was a placebo controlled trial of secondary fracture prevention comprising supplementation with calcium, vitamin D or both, found no difference in fracture rate between any of the four arms (Grant et al. 2005). The various evidence has been synthesised into a meta-analysis of prospective cohort and randomised controlled trials which showed no relationship between calcium intake, whether food alone or including supplements, and hip

fracture (Bischoff-Ferrari et al. 2007). Adherence to long term calcium supplementation may prove difficult and affect outcomes of studies and this has been addressed by a meta-analysis considering the effects of "poor" compliance (<80%) with better compliance (80% or above), which showed a lower fracture rate in the latter than in controls (Tang et al. 2007). Pulling the available data from nutritional studies into a meta-analysis is difficult on a subject such as dietary calcium intake but it is also important to look at the *hard* clinical outcome of fracture. However, Bolland and colleagues concluded that the epidemiological evidence did not support an association between dietary calcium intake and risk of fracture, and that there was no clinical trial evidence that increasing calcium intake from dietary sources prevents fractures and they also concluded that the evidence from calcium dietary supplement trials was inconclusive (Bolland et al. 2015).

Briefly reviewing epidemiological data on vitamin D, results from the NHANES survey in North America have suggested a positive relationship between circulating 25(OH) vitamin D and BMD, across all ranges of 25(OH) vitamin D in the white population. However, this association is strongest in the third to the fifth decades and less conspicuous in older adults, and the effect is not seen in black and hispanic adults, where the gradient is not so steep and tails off as 25(OH) vitamin D levels exceed 80 nmol/L (Bischoff-Ferrari et al. 2004). Comparing this epidemiological with meta-analysis of clinical trial evidence, vitamin D supplementation does not increase BMD, other than at the femoral neck, where there is a small effect (Reid et al. 2014). More recently, a secondary analysis of a clinical trial of vitamin D supplementation in older women did show an effect of supplement on BMD which was confined to participants who started with a low 25(OH) vitamin D level (Macdonald et al. 2018), implying that the rise in BMD may be the treatment of occult osteomalacia. Beyond the potential effect of vitamin D on BMD, fracture prevention remains unproven. While it has been argued that a decrease in fracture incidence in clinical trials has only been shown where a vitamin D dose of at least 800 IU/day (20 ug/day) was used (Bischoff-Ferrari et al. 2012), the Cochrane collaboration meta-analysis failed to confirm any effect of vitamin D monotherapy on fracture prevention, irrespective of dose (Avenell et al. 2014). Beyond the direct effects of calcium and vitamin D on bone and BMD, there are other considerations, including muscle function and falls risk, which will be addressed separately when considering falls.

Falls

A good starting point, when considering falls in older people is to set out our definition. Specifically a fall occurs when an individual "inadvertently comes to rest on the ground, floor or other lower level, excluding an intentional change in position to rest in furniture, wall or other objects" (World Health Organization et al. 2008). Approximately a third of falls are believed to result in a requirement for medical attention (Berry and Miller 2008), with falls resulting in injury, including fractures, as well as longer term health issues such as fear of falling and even death and older age a critically important predictor of adverse outcome (World Health Organization

et al. 2008). In the context of osteoporosis, we usual exclude falls from greater than standing height, which are likely to result in greater force being applied to the skeleton and an increased likelihood of fracture, even in the absence of osteoporosis. We talk of *low trauma fractures* of the appendicular skeleton (arms, legs, shoulder and pelvis) which are often associated with a fall, while vertebral fractures may be occult or be recognised as acute severe back pain with no experience of fall or injury. As both falls and osteoporosis are common in older people, it is an important challenge to evaluate their independent risk factors as well as how they can influence one another. A range of models have been suggested for considering falls risk with the WHO recommending these be considered in terms of biological, behavioural, environmental and socio-economic risk factors (World Health Organization et al. 2008). Simplifying that, for this discussion, some are *intrinsic*, such as: chronic diseases, including impaired cognition, arthritis, dizziness and visual impairment; acute illness, such as delirium as well as some age-related changes, including sarcopenia and loss of muscle mass and function. *Extrinsic and environmental* factors may also be important, including the quality of domestic and public lighting, environment risks such as rugs and furniture, as well as the risks posed by pets and other sources of distraction, while simple personal matters such as footwear and access to appropriate walking aids, frames and appliances may also influence an older person's postural stability. Between 20% and 33% of older people fall each year (Peel 2011), with estimates varying greatly between study populations and methods of case finding (e.g. whether using self-reported falls rates, recall or prospective diaries with or without prompts). Older people may fall for a number of reasons, including gait and balance problems, sensory impairments (including vision and neuropathy), environmental hazards or syncope (transient loss of consciousness).

With such a range of mechanisms by which an older person might sustain a fall, interventions to prevent falls and falls-related injury have to be complex. Some of the best evidence comes from multifactorial interventions, targeting a range of culprit mechanisms for falls. The Cochrane review on falls prevention in older people living in the community found that trials which involved a strategy of case finding and onward referral resulted in an overall [95% CI] decrease in falls incidence by 18[5–29]%, whereas active intervention trials were associated with a slightly greater 26[11–39]% decrease. There were a number of effective components of multifactorial intervention most of which also incorporated exercise, including home safety assessment, which decreased falls by 23%, visual assessment (28% fewer falls), home assessment (31% fewer falls), educational intervention (54% fewer falls), ankle exercises (36% fewer falls), vibration therapy (54% fewer falls) and nutritional assessment and intervention associated with a remarkable 81% reduction in falls (Gillespie et al. 2012). It is estimated that 10–15% falls result in serious injuries with 0.2–1.5% of falls resulting in a hip fracture (Peel 2011), so an important clinical question is whether fall prevention can be shown to decrease fracture risk. Exercise interventions do appear to decrease fractures by 66 [37–82]%, albeit based on clinical trials involving only 810 participants (Gillespie et al. 2012). Unfortunately, the evidence for multifaceted interventions to prevent falls and fractures in older people in institutions (e.g. care homes and hospitals) is not as impressive. In certain

settings, vitamin D supplementation, probably with calcium, is effective in reducing the rate of falls as may exercise interventions. Multifactorial interventions to decrease the risk of falling in care settings were inconclusive, although targeted interventions can decrease falls in those at risk. (Cameron et al. 2012).

Calcium, Vitamin D and Falls

Suboptimal dietary calcium intakes and poor vitamin D status have been recognized as potential risk factors for falls and fractures. Individual studies vary in their results and so it is left to meta-analysis to synthesise the evidence. Here we also see some inconsistencies with three meta-analyses coming to different conclusions. Bischoff Ferrari concluded that vitamin D supplementation (without calcium) could decrease falls rates, so long as a dose of at least 700 IU (17.5 ug) per day is given (Bischoff-Ferrari et al. 2009a). Another meta-analysis, which included 45,782 older adults, concluded that vitamin D monotherapy was ineffective, while vitamin D with calcium was associated with a 14 [4–27]% decrease in falls incidence, with the greatest evidence of benefit seen in older women (Murad et al. 2011). In a third meta-analysis, intended to evaluate the potential value of performing further trials on vitamin D and falls prevention, 20 randomised controlled trials were included with a total of 29,535 participants. They concluded that supplementation with vitamin D, with or without calcium, did not reduce falls by 15% or more, based on current trial evidence, which is consistent with the conclusions of Murad (Bolland et al. 2014). With a rate of around 30% per annum in the general population aged over 75 years, is a decrease by 15% a significant effect? Here we encounter one of the challenges of intervention in falls research. It seems highly unlikely that those who are at risk of falls can be *cured*, except perhaps in the rare cases of transient loss of consciousness due to a medically treatable cause, such as heart block. When one reviews the distribution of fall frequency in an older population, some people will fall frequently (daily in some cases) while others may be extremely rare fallers. A 15% decrease in falls for a person who falls 300 times a year may not make a major impact or significantly decrease their risk of major injury or fracture. However, to prevent a fall in a person who has a 30% of falling in that year may have a much more significant impact on injury or fracture risk for them.

What about risks of intervention? A couple of vitamin D intervention studies were published over 10 years ago, using high dose vitamin D2. In one study, 100,000 IU were given every 3 months orally to care home residents with the intention of decreasing falls and fractures. Over 10 months of follow up and an average dosing of a little over 300,000 IU of vitamin D, there was a non-significant increase in risk of hip fracture (Law et al. 2006). In another study, giving 300,000 IU vitamin D2 by injection, there was a significant increase in hip fractures seen in community dwelling older people (Smith et al. 2007). These results were mostly ignored, until an Australian study of participants, known to be at high risk of falling, were given 500,000 IU as a once yearly dose to for an average of 3 years. This study showed a very high falls rate in the participants over 3 years, with 73% of those receiving

Table 16.3 Falls observed in recent studies of vitamin D supplementation

Study	Number of participants Sex Mean Age	Intervention	Dose [frequency]	Follow up in months	Fall estimate used	Result: falls rate with Vitamin D	Comments
Sanders (2010)	2317 Females 76 years	Vitamin D3 or Placebo	500,000 IU [yearly]	36	IRR & time to 1st fall	IRR=1.15 [1.02–1.30]	High falls risk group at baseline
							50% fell at 1 year
							Prospective falls questionnaire
							Early effects post-dose?
							10% difference in absolute risk with NNH of 10
Bischoff Ferrari (2016)	200 Males & Females 77 years	Vitamin D3 (2 doses) or D3+ calcifediol	24,000 IU or 60,000 IU or 24,000 IU+300 μg calcifediol [monthly]	12	Compare incidence at 6 & 12 months	More falls at higher doses, 67% vs lower dose, 48% (p = .048)	High falls risk group at baseline
							>60% fell at 1 year
							Falls NOT primary outcome.
							Good ascertainment
Smith (2017)	273 Females 66 years	Vitamin D3 or Placebo	Placebo or Low: 400 800 or Mid:1600 2400 3200 or High: 4000 4800 [daily]	12	1+ falls (%)	Placebo as reference:	60% fell at 1 year at lower 25OHD
							72% in highest quintiles for 25OHD
						Low (NS)	Falls NOT primary outcome.
						Mid-dose (fewer falls)	There was a difference in baseline fall history: 68% on low dose 27% on medium dose 100% on higher dose
						High dose (NS)	
Kay-Tee Khaw (2017) ViDA	5110 Males & Females 66 years	D3 Vs PBO	100,000 [monthly]	41	time to 1st fall	No effect	Relatively low risk population
							c.30% fell at 1 year
							Falls NOT primary outcome of the study
							No validation for falls (unlike fracture)
							Fewer completed falls questionnaires than
							fracture questionnaire

Abbreviations used: incidence rate ratio (IRR), number needed to harm (NNH), vitamin D3 (D3), not significant difference (NS)

placebo sustaining at least one fall over this period but 83% in the intervention arm falling. That is an absolute risk increase of 10% and a number needed to harm (NNH) of 10. There was also a (not significant, p = 0.06) increased risk of fracture by 26 [−1 to 59]% (Sanders et al. 2010). Table 16.3 summarises the Sanders study and more recent and relevant studies, including those of Bischoff Ferrari, Kay-Tee Khaw and Smith and Gallagher (Bischoff-Ferrari et al. 2016; Khaw et al. 2017; Smith et al. 2017). They show that there appears to be no benefit of high dose vitamin D supplementation in fall prevention. There is therefore clinical justification for treating vitamin D deficiency, with the expectation of treating the complications of osteomalacia and, for the general population of older people, there is some argument for modest vitamin D supplementation but no benefit and possibly some risk of adverse outcomes, when those at higher risk of falls are given very high doses of vitamin D, for example, in excess of 300,000 IU.

Frailty

Between the ages of 60 and 80 years, fracture risk increases by a factor of 13 but BMD explains only half of fracture risk (De Laet et al. 1997). Other factors are also very important, including previous fragility fracture and gender, as women continue to sustain more fragility fractures than men and, in the broadest sense, frailty may also explain much of the increase in fracture risk seen in the old and very old.

Frailty is a clinical state in which there is an increase in an individual's vulnerability for developing dependency with a possibly increased risk of mortality when exposed to a stressor (Morley et al. 2013). Frailty has been defined in operational terms by Rockwood using an index, which comprises a list of deficits which may be accumulated. Such aspects of health, function and social condition are markers of increasing frailty, as the greater the number of impairments, the frailer the person. The resulting frail phenotype is determined by items identified in multiple domains, reflecting multiple co-morbidities, as represented by a high aggregate score (Rockwood and Mitnitski 2007). By contrast, Fried devised a frailty phenotype, which reflects the domains of impairment seen in frailty. The clinical syndrome is evaluated functionally, using weight loss, muscle weakness, subjective physical exhaustion, slowed walking speed and physical inactivity. Three or more of these five characteristics predicts frailty (Fried et al. 2001).

The impact of frailty, whether evaluated by a frailty index or function assessment, is an increased likelihood of moving into institutional care and, ultimately, an increased mortality (Jones et al. 2005; Abellan van Kan et al. 2008). Considering skeletal health, the Study of Osteoporotic Fracture (SOF) derived a parsimonious frailty index from the available data, similar to that used by Fried but using only three criteria: weight loss of 5% or more in a year, inability to rise from a chair and a reduced energy level using data from the (self reported) geriatric depression scale (GDS) In the older population studied, frailty using the SOF criteria predicted:

- Increased risk of hip fracture in women with an odds ratio (OR) of 1.8
- Increased risk of non-spine fracture in men with an OR of 2.2
- Increased risk of falls and mortality in men (OR = 3.0) and women (OR = 2.4)
- Increased risk of disability in in men (OR = 5.3) and women (OR = 2.2) (Ensrud et al. 2008, 2009).

Sarcopenia

Sarcopenia, defined as both a loss of muscle mass and muscle function is not simply a nutritional disorder, associated with older age (Cruz-Jentoft et al. 2010). Approximately 5–13% of those aged 60–70 years are affected by sarcopenia, increasing to 11–50% for those aged 80 or above (von Haehling et al. 2010) and 20% of patients sustaining a hip fracture also have sarcopenia at presentation (Gonzalez-Montalvo et al. 2016). There is considerable overlap between sarcopenia and frailty, osteoporosis, falls and fracture risk (Landi et al. 2012) as well as a number of other chronic diseases, including insulin resistance and type 2 diabetes (Levine and Crimmins 2012), cardiovascular disease, chronic kidney disease (Honda et al. 2007) and adverse outcomes from cancer (Fearon et al. 2011). Di Monaco and colleagues found considerable overlap between frailty and sarcopenia, in patients sustaining a hip fracture, with 45% having both, 28% sarcopenia alone and only 14% having neither (Di Monaco et al. 2011).

Fracture Risk Assessment in Old Age

Looking at practical aspects of frailty, while a range of clinical risk factors contribute to fracture risk, their significance will vary with age and the presence of comorbidities, including sarcopenia and frailty. FRAX (Kanis et al. 2012) and QFracture (Cummins et al. 2011; Hippisley-Cox and Coupland 2009) can both identify fracture risk, using a range of risk factors which include glucocorticoid therapy, smoking and drinking habits and body mass index for FRAX (and an even longer list for QFracture). However, there are some practical limitations to the application of FRAX (and QFracture), particularly in the very old and frail. Firstly, there is an upper limit on age, with FRAX currently working up to the age of 90 years (QFracture up to 100). Much of the data used to create the FRAX algorithms comes from research studies, where participants will have had to give informed consent. Can we rely on such data to predict fracture risk in older adults with dementia? There are certainly data to suggest a higher prevalence of risk factors and lower BMD in older people with dementia, at least in those living in institutions (Aspray et al. 2006), as well as undertreatment of older adults with dementia (Haasum et al. 2012). There are also pragmatic problems with the potential robustness of data. Can frail older patients (with or without cognitive impairment) remember their previous

fracture history or a history of parental fracture (or do we need to depend on imperfect medical record or relatives)? Are measurements of weight and height likely to be valid (and should we use current or adult height)? Weight loss is an important independent predictor of frailty, but it is not considered in FRAX. Previous glucocorticoid usage may be common in an aged population, but the current prescription of high dose glucocorticoids is more likely to be relevant (at any age), as noted by the IOF/ECTS (Lekamwasam et al. 2012). Current smoking and alcohol consumption may be less likely among the very old and the relevance of secondary osteoporosis in this population is unknown. Having highlighted that frailty is important as a cause of fracture risk, it is disappointing that there is no clinical risk factor estimating frailty and, in particularly, aspects of the phenotype including falls, dementia, immobility or weight loss in FRAX. While alternative risk assessment tools include falls, such as QFracture, the data quality on which this algorithm is based is dubious, since routine general practice databases in the UK rarely document incident falls although (Hippisley-Cox and Coupland 2012), as discussed elsewhere in this chapter, a third of older adults will experience a fall each year.

Co-morbidities

Much has already been discussed about calcium, vitamin D and falls, although it is perhaps necessary to justify such a large contribution on this topic. The means of assessing falls incidence is critically important to the quality of the research evidence on this topic, particularly when evaluating interventions to decrease risk. However, it cannot be doubted that falls are clinically important in the aetiology of fragility fractures, particular in the frailer population. In one study of people over the age of 90 years, fractures occurred in the context of a fall in 86% of cases (Court-Brown and Clement 2009). Such injuries may be associated with comorbidities, including dementia, chronic kidney disease and diabetes mellitus (Mayne et al. 2010) due to a number of mechanisms, including dysautonomia or the adverse cardiovascular effects of multiple medications used to treat these conditions.

Although data from Holland, already cited (De Laet et al. 1997), suggest that BMD is not the main determinant of fracture risk in old age, there are a number of factors commoner in frail older people which have a negative effect on the skeleton, including immobility, specific diseases, such as cancer myeloma, and their treatment, including anti-androgen for prostate cancer, anti-oestrogens for breast cancer and thiazolidinediones for diabetes mellitus. Dementia is another important factor in older age, with 6.4% of adults over 65 years of age and 28.5% aged over 90 years affected (Lobo et al. 2000). Meta-analysis of epidemiological data suggest that fractures are commoner in older people with dementia living in the community (OR, 2.13) or institutions (OR, 1.88) (Muir et al. 2012), while the incidence of hip fractures in patients with dementia in the UK between 1988 and 2007 was 17.4/1000 patient year (a hazard ratio (HR) of 3.2 for fracture and 1.5 for fracture mortality) (Baker et al. 2011). There are a number of potential effects of dementia treatments,

with acetylcholine esterase inhibitors increasing the risk of syncopal episodes, while memantine is associated with a lower risk of falling (Kim et al. 2011). Other treatments, such as sedative drugs, are all too frequently used in the management of patients with dementia, which may be associated with an increase in fracture risk (Finkle et al. 2011).

Moderate to severe chronic kidney disease (CKD) is prevalent in 8% of the adult population (Castro and Coresh 2009) and its incidence increases with age (Van Pottelbergh et al. 2012). It is important to recognise that BMD does not predict osteoporosis or increased fracture risk as effectively in the presence of CKD-associated metabolic bone disease (CKD-MBD) (Moe et al. 2006). Distinct entities exist, including adynamic, hyperparathyroidism, osteitis fibrosa cystica, osteomalacia or mixed uraemic osteodystrophy. The presence of CKD also influences treatment choices, with bisphosphonate best avoided at low glomerular filtration rates due to an increased risk of acute kidney injury.

Polypharmacy is a common, with 57% women in the USA, aged 65 years or older treated with five or more drugs (12% with 10 or more!) (Kaufman et al. 2002). As already discussed, the prescription of many drugs to frail older patients potentiates the risk of adverse effects on falls risk, postural stability, calcium homeostasis and bone health, with diuretics, sedatives, glucocorticoids and proton pump inhibitors frequent culprit medications. Decision-making about treatment may also be impaired, with the patient lacking capacity to make informed choices and balancing risks versus benefits. Frail older people may struggle to identify adverse effects and become dependent on others to help in monitoring their treatment.

For those unfortunate enough to sustain a fracture, surgery may be more difficult due to presence of comorbidities, such as delirium at the time of surgery which is associated with a greater postoperative mortality (Mitchell et al. 2017). Nutrition warrants special mention as active nutritional support with dietary supplements and assisted feeding may help mitigate the risks associated with low body mass index (BMI), a postoperative catabolic state, sarcopenia and immobility. The establishment of such strategies has proven beneficial in randomised controlled trials of postoperative and rehabilitation care to improve nutrition (Duncan et al. 2006), resulting in decreased rates of hospital and nursing home admissions after hip fracture, when targeted with exercise, falls prevention, home safety and polypharmacy. (Singh et al. 2012)

Care Homes

As frailty indices predict, many frail older people are admitted to residential and nursing homes, where their physical state and health needs may be supported. Hospital admission rates are greater for this group, particularly those living in residential care, who have a hospital admission rate of 312/1000 per year compared with an age-matched population rate from home of 190/1000 per year (Godden and Pollock 2001) Fractures are also commoner in care homes, with a relative risk (RR)

for fracture of 2.9 [2.5–3.3], equating to 11% p.a. in Residential Care and, for hip fractures, the RR is 3.3 [2.6–4.2], a rate of 3.6% p.a. for residential care homes (Brennan nee Saunders et al. 2003; Godden and Pollock 2001). In one study of 392 care home residents in the UK with a mean age of 85 years, peripheral dual energy X-ray absorptiometry (pDXA) was used to evaluate the prevalence of osteoporosis in residential and nursing home residents (as many were unable to travel). Osteoporosis was present in 69%, with a mean Z-score of −0.96 ± 0.20. However, despite the evidence of high fracture incidence and prevalent osteoporosis, many were left untreated with 2.4–12.6% receiving calcium and vitamin D supplementation and less than 2% receiving bisphosphonate therapy (Aspray and Francis 2006). However, practice is changing and the targeted treatment of older people who are frail and living in residential and nursing homes is likely to have benefits on fracture prevention.

Fracture Summary

While older age is the greatest determinant of fracture risk, other factors, relating to frailty, are also important, particularly with regard to falls and fractures as well as mortality and the likelihood of institutionalised care. In practice, common morbidities associated with frailty include both physical and cognitive impairments, which influence treatment options, response to treatment and outcomes of rehabilitation. Care homes are an important target for the identification of frail older people at risk of falls and fractures, and future interventions should focus on preventing or reversing frailty to prevent fractures. However, there will always be fragility fractures and, in order to optimise outcomes for the frail, we must promote treatment in this group with better adherence from both carers, patients and practitioners, who can be fatalistic about preventative strategies and treatment, so improvements are also needed for rehabilitation in this group.

Conclusion and Future Direction

We have come a long way from the 1980s to 1990s, shifting the clinical assessment and treatment of osteoporosis from concerns about the menopause and early postmenopausal period. Focus has moved from the management of low BMD in women in their sixth decade to the health burden and much greater fracture risk associated with osteoporosis in older women and also men aged 80 years and above. We are learning about bone quality beyond the naïf model of bone mineral density, identified using DXA, as new technologies give more information about microstructure, which contribute independently to bone strength. Epidemiological evidence confirms that non-skeletal factors can tell us more than BMD alone about individuals'

fracture risk and simple, practical questionnaire-based tools can be used to evaluate patients.

We still need to target osteoporosis in old age more effectively. The evidence around optimal nutrition is confusing, as it appears that for both calcium and vitamin D, while some may be good, much more is not necessarily better. There are links between falls, muscle function, frailty and multiple comorbidities and it may be possible to intervene to decrease fracture risk, using comprehensive interventions probably incorporated within comprehensive geriatric assessment (CGA) (Jones et al. 2005). However, beyond risk assessment and case finding, there are two areas, not covered here, which require major development. Firstly, we need effective interventions, likely to be pharmacological, to prevent fractures, which are well tolerated with few adverse effects in a frail population. Finally, we have to accept that, even with the most effective treatments available, older people will fall and fracture their bones, and we need to ensure that the potentially devastating experience of surgery and rehabilitation is as good as it can be. Innovations such as the hip fracture database can highlight where outcomes are good and where patient care could be improved (Neuburger et al. 2018; Johansen et al. 2017).

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