BONE CARE FOR THE POSTMENOPAUSAL WOMAN

www.iofbonehealth.org

International Osteoporosis Foundation

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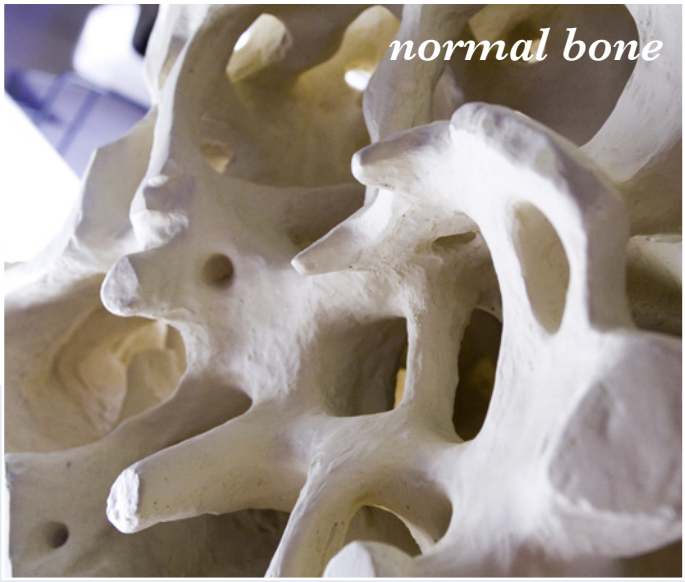

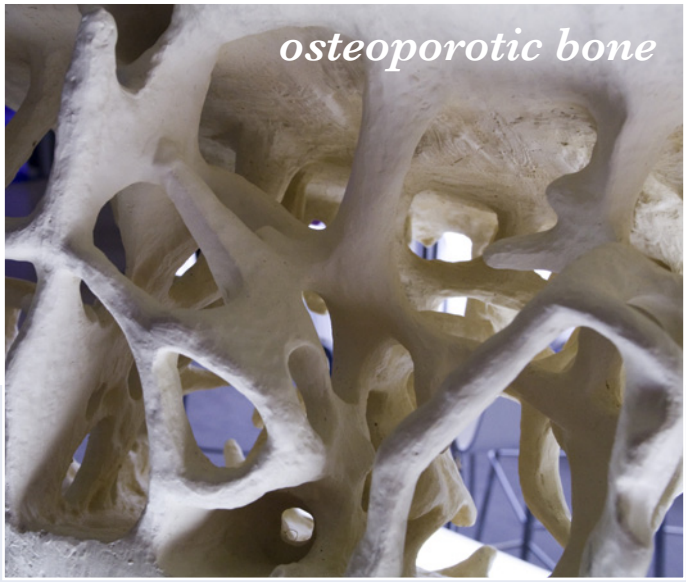

WHAT IS OSTEOPOROSIS?

Osteoporosis is a disease characterized by low bone mass and deterioration in the microarchitecture of bone tissue, leading to an increased risk of fracture. Osteoporosis occurs when the bone mass decreases more quickly than the body can replace it, leading to a net loss of bone strength. As a result the skeleton becomes fragile, so that even a slight bump or fall can lead to a broken bone, (referred to as a fragility fracture). Osteoporosis has no signs or symptoms until a fracture occurs – this is why it is often called a 'silent disease'.

Osteoporosis affects all bones in the body; however, fractures occur most frequently in the vertebrae (spine), wrist and hip. Osteoporotic fractures of the pelvis, upper arm and lower leg are also common. Osteoporosis itself is not painful but the broken bones can result in severe pain, significant disability and even mortality. Both hip and spine fractures are also associated with a higher risk of death - 20% of those who suffer a hip fracture die within 6 months after the fracture.

A COMMON DISEASE

It is estimated that worldwide an osteoporotic fracture occurs every three seconds. At 50 years of age, one in three women and one in five men will suffer a fracture in their remaining lifetime. For women, the risk of hip fracture is higher than the risk of breast, ovarian and uterine cancer combined. For men, the risk is higher than the risk for prostate cancer.

Approximately 50% of people with one osteoporotic fracture will have another, with the risk of new fractures rising exponentially with each fracture.

A GROWING PUBLIC HEALTH PROBLEM

The risk of sustaining a fracture increases exponentially with age due not only to the decrease in bone mineral density, but also due to the increased rate of falls among the elderly. The elderly represent the fastest growing segment of the population. Thus, as life expectancy increases for the majority of the world's population, the financial and human costs associated with osteoporotic fractures will increase dramatically unless preventive action is taken.

FOREWORD

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BONE HEALTH MATTERS TO WOMEN AND THEIR FAMILIES

Postmenopausal women throughout the world are facing an ever increasing burden of responsibilities; as caregivers to the young and old, bread winners preparing for retirement and contributors to the welfare of the communities in which they live. Another, more insidious, burden is being imposed upon mothers and grandmothers, sisters and aunts, and wives and partners. A burden that is becoming ever more prevalent, on every continent, amongst hundreds of millions of older women, right now. The burden in question is osteoporosis, the most common bone disease. Osteoporosis, quite literally, can shatter women's lives.

One in three women over the age of 50 will suffer a fracture caused by osteoporosis. Every reader will know a family member or friend who has suffered an osteoporotic fracture; a 55 year old sister who slipped on the ice and broke her wrist, a 65 year old mother - who has been losing height – who suffered an excruciating vertebral crush fracture whilst lifting a box of books, or a 78 year old grandmother who tripped over a telephone cable in the night and broke her hip. All of these women's lives will be seriously affected by these injuries.

Because osteoporosis is so common, every single woman alive today must come to recognise that bone health really matters to them. This report describes the key actions women can take, both before and after the menopause, to minimise their risk of suffering debilitating and painful fractures. Postmenopausal women provide the back-bone to families throughout the world; maintaining a strong skeleton will enable them to continue to do so.

BONE HEALTH MATTERS TO HEALTHCARE PROFESSIONALS AND SYSTEMS

During the next two decades, almost half a billion people will reach retirement age. As this demographic shift ensues, the demands placed upon our healthcare systems, and upon the professionals who provide care within them, will be manifest on an unprecedented scale. Crucially, clinicians throughout the world know that osteoporotic fractures are amongst the most preventable outcomes of all chronic disease.

A clear consensus has emerged amongst osteoporosis experts, geriatricians, orthopaedic surgeons and other specialties that a systematic approach to fracture prevention must be implemented on a global scale. Leading professional organisations all advocate that when postmenopausal women suffer an osteoporotic fracture, we should always respond to the first fracture to prevent the second and subsequent fractures. With the advent of fracture risk assessment calculators, doctors now have the tools to go further, and systematically identify those individuals who have not fractured yet, but are at considerably increased risk of doing so in the near future. Bone health matters to healthcare professionals because they have the expertise, and desire, to prevent their patients from suffering fractures.

BONE HEALTH MATTERS TO POLICYMAKERS AND THEIR GOVERNMENTS

As our population ages, policymakers are faced with an overwhelming array of competing priorities for finite healthcare resources. The key issue for policymakers to recognise is that osteoporosis is a condition where better care translates to better outcomes and significantly reduced costs. If the right evidence-based policies, reimbursement criteria and implementation strategies are in place, a substantial body of evidence demonstrates that fracture incidence will be reduced, and the costs associated with fracture care avoided. Bone health matters to policymakers, because if it doesn't, the costs of fracture care will simply continue to escalate, and consume budgets that will be needed to cope with the tsunami of need fuelled by retirement of the baby boomers.

WHY BONE HEALTH MATTERS

WOMEN ARE THE BACK-BONE OF FAMILIES THROUGHOUT THE WORLD

In all countries and all cultures, women play a vital role in our main social institution, the family. As the world's population ages, the demands placed upon older women in particular are set to increase. The expression 'sandwich generation' has come into common parlance to describe those people who care for their ageing parents while supporting their own children. Indeed, the notion of a 'club sandwich generation' has been coined to describe those playing a supporting role simultaneously to ageing parents, adult children and grandchildren. A growing body of evidence documents the prevalence and impact of care giving on older women in many countries and in a range of circumstances:

- **Australia**
  A quarter of women aged 45-64 years are carers, of which 7% are primary carers[1].

- **Brazil**
  Women comprised 78% of family caregivers of elderly patients on haemodialysis and peritoneal dialysis in a Brazilian study on the impact of caring on quality of life of carers[2].

- **Canada**
  Amongst the 1.7 million Canadian adults aged 45-64 who provide informal care to seniors, women dedicate twice as much time to carer tasks as men[3].

- **Korea**
  On account of limited institutional provision of care services and facilities, in a study in Kwangju, South Korea, 62% of care givers were women[4].

- **Mexico**
  Women have been documented to play the major care giving role in many situations, including care giving for children with cerebral

palsy[5], for geriatric patients[6] and for cancer patients[7].

- **Spain**
  Seventy percent of Spanish women over the age of 65 care for their grandchildren and 22% of them do so every day[8].

- **Chinese Taipei**
  The cultural norm in Chinese Taipei is to care for family members who are disabled or ill[9]. A study of caregivers of persons with stroke or Alzheimer's disease reported that 75% were women aged 52 years on average[10].

- **United Kingdom**
  About 25% of women aged 50-59 years in Britain provide some unpaid care[11].

- **USA**
  In the United States, 75% of caregivers are women[12]. Forty three percent of carers are at least 50 years of age and 61% of family caregivers are women[13].

THE SOCIO-ECONOMIC IMPACT OF FRAGILITY FRACTURES

Osteoporosis is the most common bone disease and is manifest in the form of fragility fractures, also referred to as low or minimal trauma fractures. Fragility fractures usually occur as a result of a fall from standing height and are very common; 1 in 3 women over 50 years of age will suffer one[15,16], as will 1 in 5 men[17]. Worldwide, during the year 2000, there were an estimated 9 million new fragility fractures, of which 1.6 million were at the hip, 1.7 million at the wrist, 0.7 million at the humerus and 1.4 million symptomatic vertebral fractures[18]. Overall, 61% of fractures occurred in women, including 70% of hip fractures.

In recent years the International Osteoporosis Foundation (IOF) has conducted a series of regional audits to ascertain the impact that osteoporosis is having currently – and will have in the future - upon older people and healthcare systems worldwide. These data, in addition to major studies conducted in North America, reveal the immense and growing burden of osteoporosis and fractures in all regions of the world on the map overleaf.

To better understand the challenges to the health and well-being of women in Mexico, it is important to acknowledge that the family is considered the most important value in Mexican culture, and that the woman is the essential unifying element within the family. Within the family, women play the most significant role as socialization agent and caregiver.[14]

North America As recently highlighted by the 2Million2Many Campaign of the U.S. National Bone Health Alliance[26], an evaluation of the incidence and costs of osteoporosis for the period 2005-2025 concluded that 2 million fragility fractures occur annually in the United States[27]. The proportion of fractures at skeletal sites is vertebral (27%), wrist (19%), hip (14%), pelvis (7%) and other (33%). Whilst hip fractures represent only one seventh of the total number of fractures, they accounted for 72% of total costs. More recent studies report that the age-adjusted incidence of hip fractures in the United States has been declining since the mid-1990s[28, 29]. Whilst this is welcome news, the total number of hip fractures occurring continues to present an enormous burden on older Americans and U.S. healthcare systems, primarily Medicare. Although availability of effective osteoporosis medications is coincident with the beginning of the attenuation of hip fracture rates, levels of usage – particularly in high risk patients - cannot fully account for the observed reduction. A similar phenomenon has been observed in Canada[30], where around 30 000 Canadians break their hip every year[31]. The authors of these studies conclude that there remains huge scope and need to improve fracture prevention efforts.

Over the next 20 years, *hip fracture incidence will* celebrate their 65th birthday. in the West and presents a health systems

Latin America[25] One of the most startling findings of the recent IOF Audit for Latin America was the dramatic ageing of the populations in the 14 countries evaluated. Currently, the proportion of the populations aged 50 years and over is between 13% and 29%. By 2050, these figures are estimated to increase to between 28% and 49%. The 280% estimated increase in those aged 70 years and over is set to fuel an enormous rise in the prevalence of osteoporosis and incidence of fragility fractures. In Mexico, the number of hip fractures is expected to rise from almost 30 000 in 2005 to more than 155 000 by 2050. Similarly in Argentina, the current incidence of hip fracture at 34 000 cases per year is expected to triple by 2050. In 2006, the direct cost for acute medical care of hip fractures in Mexico approached US$100 million; by 2025 these costs are projected to increase to between US$213 million and US$466 million and by 2050, to between US$555 million to US$4.1 billion, according to different projections.

Middle East and Africa[21] By 2050, the proportion of the population of this region aged over 50 years is expected to increase by 25% to 40%. As a direct result, the projected increase in the incidence of hip fracture is amongst the highest in the world. Turkey provides a useful illustration; 24 000 cases of hip fracture occurred amongst Turks aged over 50 years in 2010, which is expected to increase by 50% by the end of the current decade.

European Union[19] This report presents fracture epidemiology for the EU27 countries. The number of new fractures during 2010 in the EU was 3.5 million, comprising approximately 610 000 hip fractures, 520 000 vertebral fractures, 560 000 forearm fractures and 1.8 million other fractures. Two thirds of all incident fractures occurred in women. The cost of osteoporosis, including pharmacological intervention in the EU in 2010 was estimated at €37 billion. Uptake of individual treatments differs between regions in Europe. In general, Southern Europe shows a higher uptake of osteoporosis drugs. There is a marked variation in the availability of bone densitometry, its cost and service provisions in the EU and a majority of countries have insufficient resources to implement practice guidelines.

450 million people will

On account of this, absolute

remain high and costly

major threat to financing of

in the East.[32]

Eastern Europe and Central Asia[20] Fourteen million Russians currently have osteoporosis. By 2050, 56% of the population will be over 50 years of age, so the disease burden will increase significantly in the coming decades. The number of hip fractures in the Russian Federation is predicted to increase by 23% by 2030, reaching 144 000 cases annually. There is a stark lack of post-fracture hospitalization, with only 13% of hip fracture patients undergoing surgical repair. Consequently, post-hip fracture mortality during the first year after fracture reaches approximately 50% in many Russian cities.

Asia[22] In 1995, 5.3% of the population living in Asia was aged 65 years and over; this is projected to increase to 9.3% by 2025, representing a 75% increase for a population of several billion people. In 2009, there were 167 million people aged over 60 years living in China, which will rise to 480 million by 2050[23]. Almost 700 000 hip fractures occur annually in China. Alarmingly, from 2002 to 2006, hip fracture rates among those over 50 years of age in Beijing increased by 58% in women and 49% in men[24]. Urbanization and changes in lifestyle are proposed as the primary reasons for such a rapid change. In India, 36 million people already have osteoporosis. By 2050 more than 50% of all osteoporotic fractures will occur in Asia. In terms of costs, projections for China illustrate the financial burden that is looming across this region. In 2006, US$1.6 billion was spent on hip fracture care in China; this is projected to rise to US$12.5 billion by 2020 and $265 billion by 2050.

THE IMPACT OF FRACTURES ON QUALITY OF LIFE

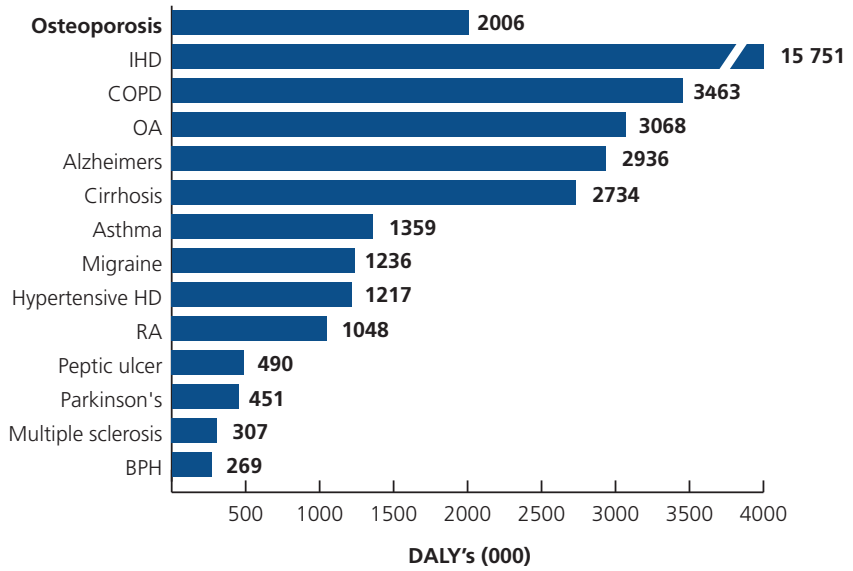
Fragility fractures exact a terrible toll on the quality of life of postmenopausal women across the world. The global burden of osteoporosis can be quantified by disability adjusted life years (DALYs)[33], which are widely used to measure the impact of a disease on the sufferer's quality of life[34]. In 2000, the total DALYs lost that were attributable to fragility fractures was 5.8 million. This accounts for 0.83% of the global burden of non-communicable disease[18]. Fragility fractures account for the loss of 2 million DALYs in Europe every year. To put this into context, *figure 1* shows the number of DALYs in Europe in 2002 for osteoporosis compared to other major diseases. With the exception of lung cancer, fractures caused by osteoporosis account for more combined deaths and morbidity than any cancer type.

Around the globe, the findings of the IOF regional audits regarding the impact of fragility fractures on quality of life in older women are truly astounding. This is particularly the case for both hip and spine fractures. In Russia, the fact that 87% of hip fracture patients do not undergo surgical repair has appalling consequences for survivors[20]; 33% remain bed-ridden, 42% have very limited activities, only 15% can ambulate outside and just 9% return to their previous level of daily activities.

Similarly, in Kazakhstan and Georgia less than 50% and 25% of hip fracture sufferers undergo surgical repair, respectively. The Middle East and Africa Audit[21] reported that mortality after hip fracture may be 2-3 times higher in this region than in Western populations. Amongst women aged over 80 years in Latin America, 38% had a vertebral fracture[25]. Given that 1 in 5 women with a vertebral fracture will sustain another one within twelve months[35], implementation of preventive measures should be a priority for health authorities in the region[36].

Worldwide, osteoporosis is significantly compromising the quality of life of countless postmenopausal women.

FIGURE 1 Burden of diseases estimated as disability-adjusted life years (DALYs) in 2002 in Europe[18].



WITHOUT PROPER SURGICAL TREATMENT, HIP FRACTURE PATIENTS ARE INVARIABLY LEFT BEDRIDDEN AND UNABLE TO WALK. THIS RUSSIAN PATIENT SUFFERED A FRACTURE OF THE FEMUR (HIP) SEVERAL YEARS AGO. SHE DID NOT RECEIVE SURGICAL TREATMENT, OR TREATMENT OF ANY KIND. NOW, EVEN SEVERAL YEARS LATER, SHE IS UNABLE TO WALK. TWICE A DAY, EVERYDAY, HER HUSBAND PUSHES HER IN A WHEELBARROW ALL THE WAY TO TOWN. THIS WAY SHE IS AT LEAST ABLE TO LEAVE THE HOUSE AND MAINTAIN SOME SOCIAL CONTACT.

POSTMENOPAUSAL WOMEN ARE AT GREATEST RISK

Menopause commonly occurs between age 50 and 53 years in women from Europe and North America, and as early as age 42 years in populations from Latin America and Asia[37]. Postmenopausal women are at high risk of developing osteoporosis and suffering fractures on account of the rapid bone loss which occurs with the onset of menopause[38-40]. As illustrated in *figure 2*, in females, bone mass achieves a peak in the mid-twenties, remains relatively stable thereafter until the beginning of the menopause, whereupon a rapid period of bone loss ensues.

Oestrogen plays a vital role in regulating the bone turnover process throughout life. Every day, our skeletons are undergoing a process of formation and resorption; one group of cells – osteoblasts – lead formation of new bone, whilst another – osteoclasts – resorb old bone. This ongoing process ensures that the skeleton maintains its structural integrity. During most women's second 25 years of life, formation and resorption are nicely balanced such that bone renewal goes on without adversely affecting total bone mass. However, as women become oestrogen deficient when menses cease, the equilibrium is lost with bone resorption exceeding bone formation. This imbalance is particularly evident in trabecular bone. In addition to oestrogen deficiency, reduced intestinal calcium absorption, increases in urinary calcium losses, and loss of androgenic, bone protective hormones produced by the ovaries also have an adverse effect on bone health[41-43]. Menopause-induced bone loss is most severe where there is an acute cessation of ovarian function, be-it due to surgery, or from the use of aromatase inhibitor therapy in cancer patients[44-47].

The age-specific incidence of fragility fractures illustrated in *figure 3*, correlates with two factors; postmenopausal bone loss and the increasing propensity to suffer falls as women enter their eighth decade[48]. The pattern and site for classical osteoporotic fractures reflect the earlier and more pronounced loss at skeletal sites most enriched in trabecular bone; that is distal forearm and spine, followed by the hip. This is a result of the larger bone surface and higher rates of skeletal remodelling in trabecular bone.

The increase in fracture risk as women age is quantified in *table 1*. This demonstrates that the vast majority of fractures occur amongst women aged over 65 years and reinforces the importance of a fragility fracture as a predictor of future fracture risk[50]; **fracture begets fracture**.

TABLE 1 Five-year risk of first and subsequent fractures in women at any skeletal site[50].

Age (years)	First (%)	Subsequent (%)
50-54	1.9	2.8
55-59	2.7	4.2
60-64	4.1	8.9
65-69	6.2	13.5
70-74	9.1	17.6
75-79	13	23.5
80-84	17.1	28.4
85-89	27.9	40.2
90 +	49.1	61.6

FIGURE 2 Bone mass rapidly decreases with the onset of the menopause[38-40].

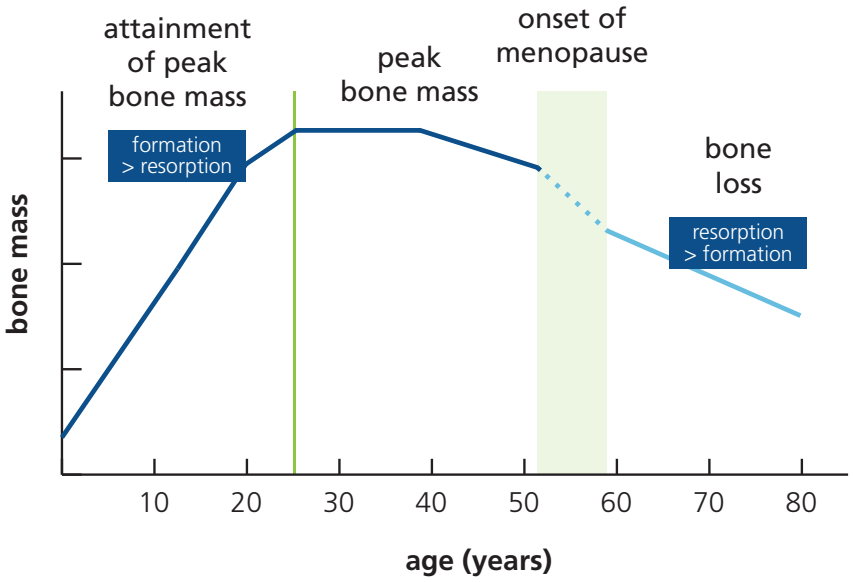
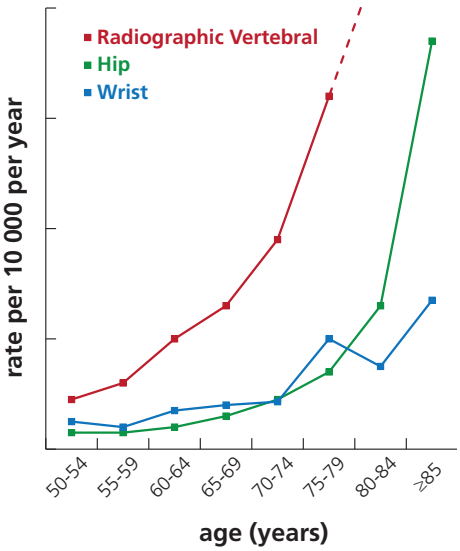


FIGURE 3 Age-specific incidence of fragility fractures for women[49].



HOW TO REDUCE OSTEOPOROSIS AND FRACTURE RISK

A growing body of evidence provides guidance for women and their health care providers on how their risk can be reduced. While peak bone mass is highly genetically determined, after 65 years of age genetics play a diminishing role in bone loss[51]. For the half a billion people who will celebrate their 65th birthday during the next two decades[52], this observation highlights the importance of the following lifestyle measures in maintaining a healthy skeleton. An individual's risk of developing osteoporosis and fragility fractures is determined by a number of factors, some of which can be changed (e.g. exercise, nutrition and smoking) while others cannot (e.g. family history, age at menopause and the presence of diseases such as rheumatoid arthritis). The modifiable risk factors will be considered first.

EXERCISE

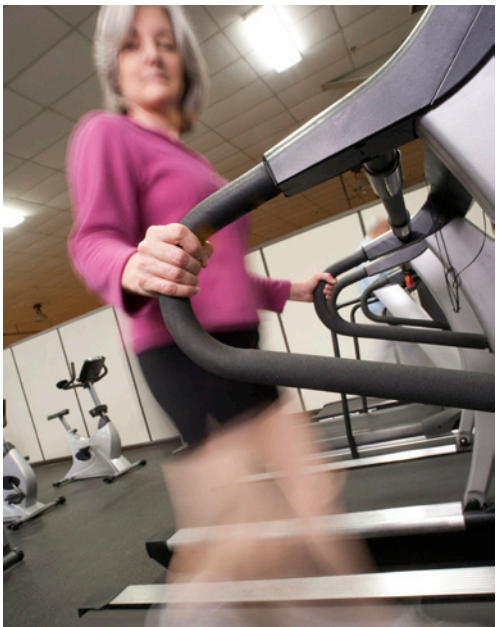
Studies have shown that individuals with a sedentary lifestyle are more likely to have a hip fracture than those who are more active. For example, women who sit for more than nine hours a day are 43% more likely to have a hip fracture than those who sit for less than six hours a day[53].

Exercise has been shown in randomised controlled trials to lead to small but statistically significant increases in bone mineral density (BMD) of the order of 1-2%[54, 55]. The recently published Osteoporosis Australia strategy 'Building healthy bones throughout life' reached the following conclusions on the role of exercise for older adults and individuals with low bone mass[56]:

- The positive effect of exercise on bone in older people is dependent upon both the type of exercise and intensity[57-59].
- Generally, resistance training becomes more beneficial as one ages.
- For fragility fracture sufferers, exercise programmes have been shown to assist recovery of function[60], prevent recurrent injurious falls[61] and improve quality of life[62].

The main benefit of exercise appears to be the associated reduction in risk of falling. Bischoff-Ferrari and colleagues compared extended physiotherapy to standard physiotherapy (PT) for elderly patients who had broken their hip[63]. The extended group received 60 minutes PT per day during their acute care compared to half that for the standard group, with the aim of supporting patients to adhere to a 30 minute per day home exercise programme after discharge from hospital. The rate of falls for the extended PT group was 25% lower than the standard group. A similar result was reported previously by Campbell and colleagues for community dwelling women aged 80 years and over in New Zealand[64]. After a year, the rate of falls in the home-based exercise group was half that of the control group.

Exercise programmes need to be highly tailored for the individual dependent upon whether they have osteoporosis, are highly prone to falling or are frail.



IN OLDER ADULTS, WEIGHT-BEARING AND MUSCLE-STRENGTHENING EXERCISES ARE ESSENTIAL FOR THE MAINTENANCE OF BONE AND MUSCLE HEALTH.

Exercises to build strong bones[65, 66]

FOR HEALTHY POSTMENOPAUSAL WOMEN WHO DO NOT HAVE OSTEOPOROSIS:

Besides maintaining bone strength, the main goal of exercise therapy in postmenopausal women is to increase muscle mass in order to improve parameters of muscle function such as balance and strength, which are both important risk factors for falls and - independent of bone density – risk factors for fractures.

Exercise should be tailored to the individual's needs and capabilities. Overall, most people should aim to exercise for 30 to 40 minutes three to four times each week, with some weight-bearing and resistance exercises in the programme. The International Osteoporosis Foundation and the U.S. National Osteoporosis Foundation recommendations on exercise are available at *http://www.iofbonehealth.org/exercise-recommendations* and *http://www.nof.org/articles/238*, respectively.

Examples of weight-bearing exercises include:

- Dancing
- High-impact aerobics
- Hiking
- Jogging/running
- Jumping rope
- Stair climbing
- Tennis

Examples of muscle-strengthening exercises include:

- Lifting weights
- Using elastic exercise bands
- Using weight machines
- Lifting your own body weight
- Standing and rising on your toes

Balance, posture and functional exercises also have an important role to play:

- Balance: Exercises which strengthen the legs and test your balance (e.g. Tai Chi) can reduce falls risk[67]
- Posture: Exercises to improve posture and reduce rounded shoulders may reduce fracture risk, particularly at the spine[68]
- Functional exercises: Exercises which help with everyday activities[63]

SPECIFIC CONSIDERATIONS FOR WOMEN WITH OSTEOPOROSIS[69]:

An exercise programme for people with osteoporosis should specifically target posture, balance, gait, coordination, and hip and trunk stabilization rather than general aerobic fitness. Such a programme was developed by Carter and colleagues in Canada and participants experienced improvements in dynamic balance and strength[70].

Several exercises are not suitable for people with osteoporosis:

- Sit-ups and excessive trunk flexion can cause vertebral crush fractures.
- Twisting movements such as a golf swing can also cause fractures[71].
- Exercises that involve abrupt or explosive loading, or high-impact loading, should be avoided.
- Daily activities such as bending to pick up objects can cause vertebral fracture[72].

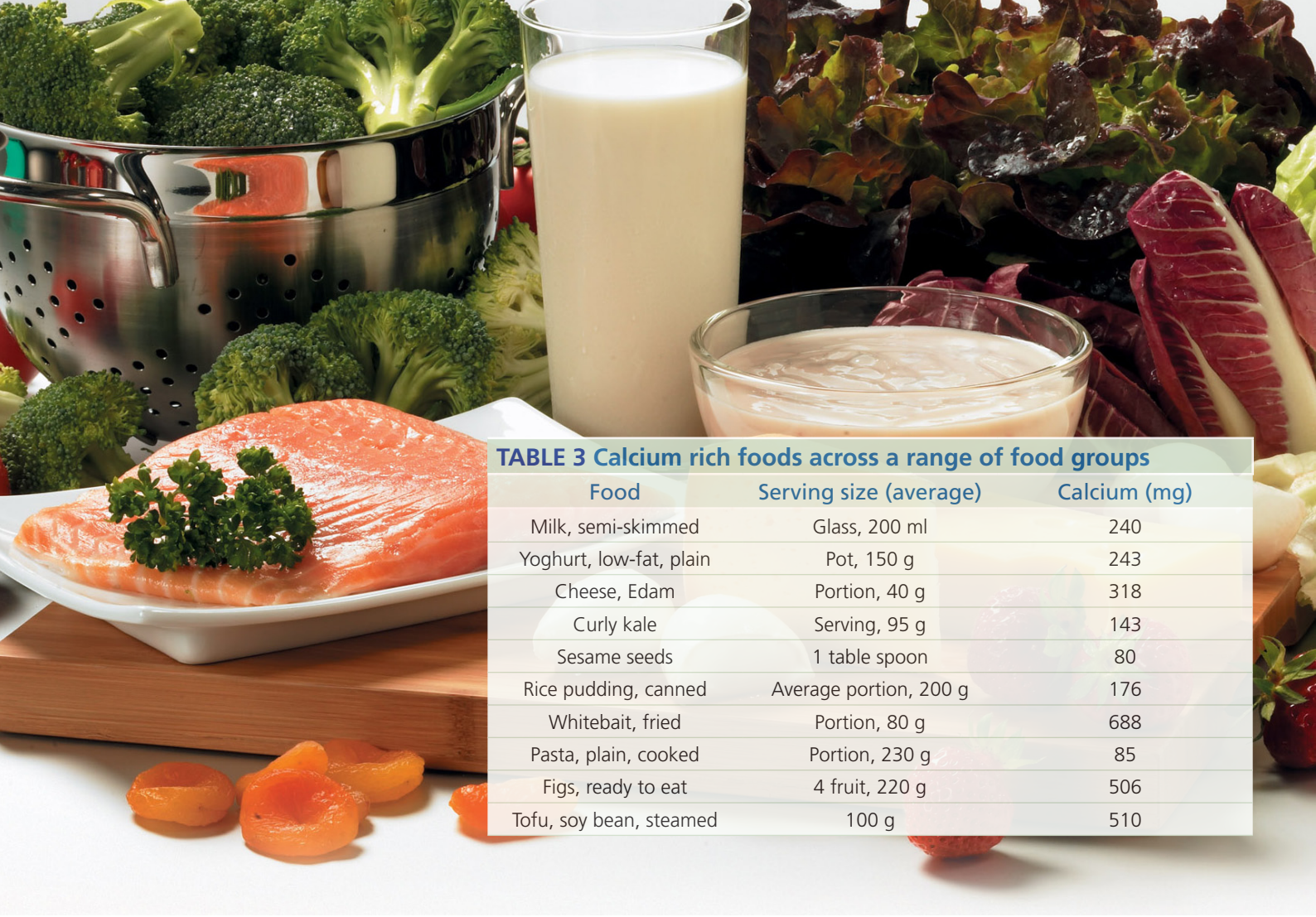


TABLE 3 Calcium rich foods across a range of food groups

Food	Serving size (average)	Calcium (mg)
Milk, semi-skimmed	Glass, 200 ml	240
Yoghurt, low-fat, plain	Pot, 150 g	243
Cheese, Edam	Portion, 40 g	318
Curly kale	Serving, 95 g	143
Sesame seeds	1 table spoon	80
Rice pudding, canned	Average portion, 200 g	176
Whitebait, fried	Portion, 80 g	688
Pasta, plain, cooked	Portion, 230 g	85
Figs, ready to eat	4 fruit, 220 g	506
Tofu, soy bean, steamed	100 g	510

NUTRITION – CALCIUM, VITAMIN D AND OTHER NUTRIENTS

Calcium

Practically all of our calcium resides in our bones – 99% of the 1 kg of calcium found in the average adult body – so calcium is a major building block of our skeleton. The calcium in our bones also acts as a reservoir for maintaining calcium levels in the blood, which is essential for nerve and muscle function. Throughout the course of our lives, the amount of calcium we need changes. As the skeleton rapidly grows during the teenage years, calcium needs are high. As the body's ability to absorb calcium declines with advancing age[73], the requirements of older people also increase. *Table 2* provides information on recommended calcium intake for several countries and from global organizations.

During the last few years there has been significant debate in the scientific literature on how best individuals can ensure they have adequate intake of calcium to support a healthy skeleton. A clear message from this debate is that diet should be the primary source of calcium. *Table 3* highlights a list of 10 calcium rich foods across a range of food groups.

Studies from Australia[80] and the United States[78] have reported a significant gap between the recommended and actual calcium intake in the population. For older women in the United States this gap is of the order 450 mg per day[78]. On account of this, calcium supplementation has played a role to ensure older individuals are calcium replete. Whilst calcium intake at the recommended levels is considered safe, considerable attention in the media has focused on the safety of high dose calcium supplements in light of recent analyses. An increase in the incidence of kidney stones in women taking high dose supplements (but not men) has been reported[81, 82]. The opposite is evident for women[81] (and men[83]) achieving high calcium intake from their diet.

The current debate on the safety of high dose calcium supplements is focused upon the risk-benefit ratio in terms of the risk of cardiovascular disease. In 2008, Bolland and colleagues reported that treatment of healthy postmenopausal women with 1000 mg of supplemental calcium doubled the risk of myocardial infarction (heart attack) in comparison to women treated with placebo[84]. Other studies have reported inconsistent results, however, none have found an association between increased risk of cardiovascular disease and dietary calcium intake[85-88]. The recent Osteoporosis Australia strategy extensively evaluated this issue and concluded[56]:

"Calcium or calcium–vitamin D supplements may be beneficial for general health as well as reducing fracture risk in people who may not be getting enough calcium through their diet[89]. Nevertheless, dietary calcium is the preferred source of calcium, and calcium supplements should be limited to 500–600mg per day.

TABLE 2 Recommended daily calcium intake for several countries

Country	Age range	Calcium intake (mg)	Organization
Australia	51-70 years	1300 (RDI)	National Health and Medical Research Council[74]
	> 70 years	1300 (RDI)	
Canada	≥ 50 years	1200	Osteoporosis Canada[75]
Korea	≥ 50 years	700	Korean Nutrition Society[76]
UK	≥ 50 years	700	Department of Health[77]
USA	51-70 years	1200 (DRI)	Institute of Medicine[78]
	≥ 71 years	1200 (DRI)	
WHO/FAO	postmenopausal women	1300	WHO/FAO 2002[79]

RDI Recommended Dietary Intake • **DRI** Dietary Reference Intake

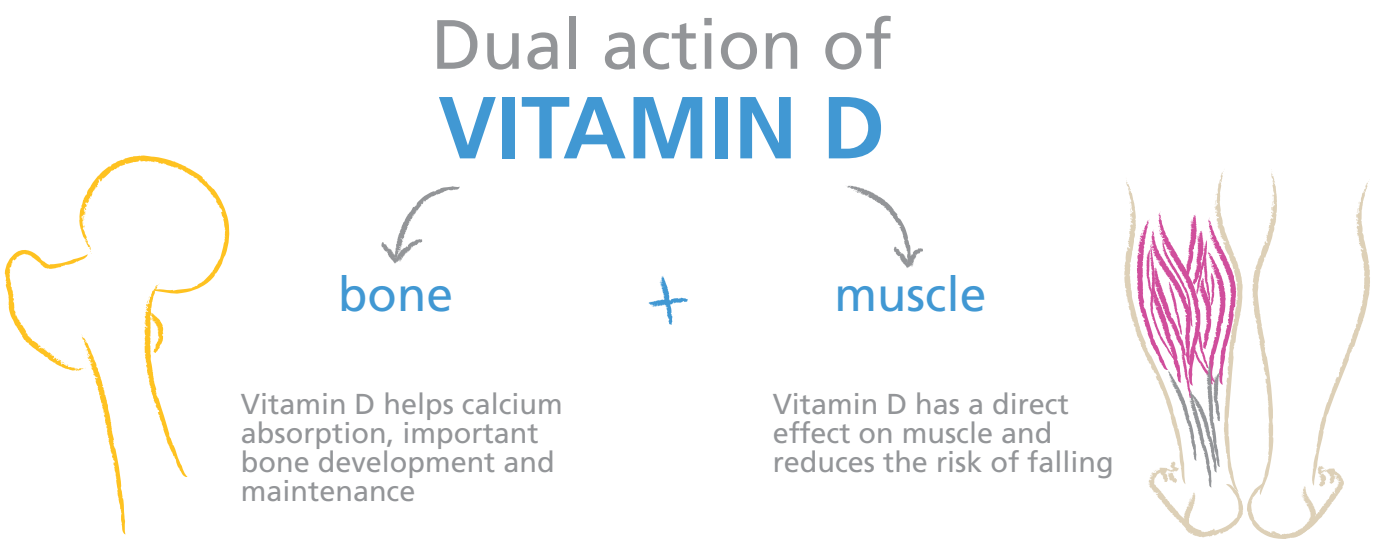
Vitamin D

Vitamin D is primarily synthesised in the skin after sun exposure and plays a crucial role in bone and muscle development, function and preservation[90]. Vitamin D can contribute to reducing fracture risk through the following mechanisms:

- Calcium homeostasis and Bone Mineral Density
  1,25-dihydroxyvitamin D (the active form of vitamin D) and parathyroid hormone (PTH) are the two most important hormones for regulation of calcium levels in the body (*see figure 4*). Serum levels of 25-hydroxyvitamin D are inversely related to serum levels of PTH and positively associated with BMD[91-93].
- Muscle performance
  Data from the Third National Health and Nutrition Survey (NHANES III) in the United States reported a correlation between lower extremity muscle performance and levels of 25-hydroxyvitamin D[94].
- Balance
  In the clinical trial setting, balance has been measured in terms of the degree of sway experienced by subjects standing on a force platform. Body sway was reduced by up to 28% amongst older study participants who received vitamin D in addition to calcium compared to those receiving calcium alone[95,96].
- Falls risk
  Vitamin D administered at doses in the range 700 – 1,000 IU per day has been associated in meta-analyses with a reduction in falls incidence of around one fifth[97, 98].
- A considerable number of randomised controlled trials have evaluated the effect of vitamin D supplementation on fracture rates in older women and men. It is generally agreed that vitamin D lowers fracture risk[78, 99], but there is currently no consensus on the serum 25-hydroxyvitamin D level needed for optimal benefit. For the general population, the level of 50 nmol/L is considered optimal[78], whereas many clinical guidelines recommend a level of 75 nmol/L[90, 99].

Low levels of vitamin D in the population are a cause of concern around the world. In 2009, an IOF Working Group published a review of global vitamin D status and determinants of hypovitaminosis D[100]. Based on a definition of vitamin D insufficiency as a level of 25-hydroxyvitamin D of <75 nmol/L

FIGURE 4 The role of vitamin D in bone health



(30 ng/ml), insufficiency was highly prevalent in all six regions studied (Asia, Europe, Middle East and Africa, Latin America, North America, and Oceania). Further, vitamin D deficiency – defined as <25 nmol/L (10 ng/ml) – was most common in the Middle East and South Asia.

In 2010, IOF published a position statement on vitamin D recommendations for older adults[90]. The estimated average vitamin D requirement for older adults to achieve a serum 25-hydroxyvitamin D level of 75 nmol/L (30 ng/ml) is 20 to 25 µg per day (800 to 1,000 IU per day). However, considerably higher doses would be needed to ensure that almost all older adults achieved the target level. In high-risk individuals, measurement of serum 25-hydroxyvitamin D is recommended. The required dose of vitamin D could be estimated based upon the notion that each 2.5 µg (100 IU) per day added will increase serum 25-hydroxyvitamin D by about 2.5 nmol/L (1 ng/ml)[101]. Re-testing after three months of supplementation is recommended for high-risk individuals to confirm that target levels have been achieved.

Protein

Body composition changes after middle age, including increases in fat mass and decreases in lean mass (i.e. muscle). One modifiable component of this sarcopenic process is dietary protein intake. The Health ABC Study in the United States evaluated body composition, weight-related health conditions and incident functional limitations in older adults[102]. Those participants in the highest quintile for protein intake lost 40% less lean mass and non-bone appendicular mass than those in the lowest quintile of protein intake. Further, the Framingham Osteoporosis Study provided evidence of the effect of dietary protein on bone loss in older people[103]. Both lower protein intake and lower animal protein intake were associated with loss of BMD at the hip and spine. Notably, the effect was comparable to that of the well documented negative effects of smoking or lower weight (4.5 kg, 10 lb) on BMD. Another study highlighted the need for individuals to achieve an adequate calcium intake in order for the beneficial effect of protein on BMD to be realised[104].

Acid-base balance of the diet

The impact of acid-base balance on bone is a comparatively new area of research. Investigation of the effect of aging on blood acid-base composition suggests that reduced renal function in older people diminishes the kidney's ability to excrete hydrogen ions in response to changes in blood pH[105]. Accordingly, healthy adults manifest a low-grade diet-dependent metabolic acidosis which increases with age. Diet can contribute to acidosis when alkali-producing fruits and vegetables are consumed in insufficient amounts to balance the intake of acid-producing foods such as cereal grains and protein. The organic acids in fruits and vegetables are metabolized to alkaline bicarbonate; cereal grains contribute phytic and other acids and protein adds acid in proportion to its content of sulphur-containing amino acids (which are metabolized to sulphuric acid).

An acidic environment has negative effects on preservation of bone in that it can impair bone forming cells[106-108], activate bone resorption[109, 110], as well as exert a direct chemical effect on bone[111].

To accommodate the need of older women for protein, the dietary acid load can be lowered by decreasing intake of cereal grains. Increasing intake of fruits and vegetables is another good option. Diets rich in fruit and vegetables have been shown to be associated with higher BMD and/or lower propensity for bone loss[112-116].

Lower protein intake is associated with loss of bone mineral density at the hip and spine. Diets rich in fruits and vegetables have been shown to be associated with higher bone mineral density.

LIFESTYLE FACTORS WITH NEGATIVE IMPACT ON BONE

Smoking

Current smokers and those who have smoked in the past are at increased risk of any fracture, compared to non-smokers[117]. Smoking is associated with several risk factors for osteoporosis including early menopause[118] and thinness[119]. Another mechanism through which smoking may impact on bone health is acceleration of oestrogen metabolism[120].

Alcohol

Alcohol taken in moderation – up to two glasses (2 x 120 ml) of wine per day - does not negatively impact on bone health. A Finnish study reported that mild to moderate alcohol intake was actually associated with greater bone mass amongst postmenopausal women[121]. A recent study suggests that the inhibitory effect of alcohol on bone turnover attenuates excessive bone turnover associated with menopause[122]. However, long-term heavy alcohol use has been shown to increase fracture risk in women and men[123]. The mechanisms by which alcohol may adversely affect fracture risk include:

- Alcohol has direct effects on osteoblasts (bone-forming cells)[124].
- Alcohol increases the endogenous

secretion of calcitonin, a hormone which suppresses resorption of bone by inhibiting the activity of osteoclasts[125]. Calcitonin also inhibits reabsorption of calcium and phosphorus in the kidney, leading to increased rates of their loss in urine.

- Heavy drinkers may have poor nutrition with respect to calcium, vitamin D, or protein[126].
- Alcohol increases the risk of falls[127] or interferes with the protective response to injury[128-130].

Maintaining a healthy weight

Leanness – defined as a body mass index (BMI) <20 kg/m^2 - regardless of age, sex and weight loss, is associated with greater bone loss and increased risk of fracture. People with a BMI of 20 kg/m^2 have a two-fold increased risk of fracture compared to people with a BMI of 25 kg/m^2 [131].
Whilst anorexia is primarily of concern in younger women, the associated malnutrition, thinness and accompanying loss of oestrogen is devastating to bone health and dental health[132].

The elderly are particularly vulnerable to malnutrition and it is important that seniors, or their caregivers, ensure sufficient caloric intake. As they age, individuals may be less capable of making the effort to prepare balanced meals, have less appetite, or suffer from chronic diseases and use medications that may impair appetite. A taskforce in the UK found that 14% of older people are at risk of malnutrition[133]. An evaluation based on BMI showed that in the UK 5% of older people living at home are underweight (BMI <20kg/m^2), a figure that rises to 9% for those with chronic diseases.

AS WELL AS SUFFICIENT CALCIUM, VITAMIN D AND PROTEIN, A 'BONE HEALTHY DIET' SHOULD ALSO BE RICH IN FRUITS AND VEGETABLES.

INDIVIDUAL RISK FACTORS

To enable women and their health care professionals to identify which individuals are at high risk of suffering osteoporotic fractures, awareness of the following non-modifiable risk factors is paramount.

PREVIOUS FRAGILITY FRACTURES

Osteoporosis is a chronic disease which is manifested in the form of fragility fractures – defined as fractures which occur as a result of low trauma, and usually result from a fall from standing height. Fragility fractures are very common: 1 in 3 postmenopausal women will suffer at least one during their remaining lifetime[15, 16]. Several studies have evaluated future fracture risk associated with suffering fractures at various skeletal sites. Two meta-analyses reported that a prior fracture at any site is associated with a doubling of future fracture risk[134, 135]. From the obverse perspective, about half of patients presenting with hip fractures have previously broken another bone before breaking their hip[136-139].

The 16% of postmenopausal women whom have already suffered a fragility fracture are the most readily identifiable group of individuals at high risk of suffering second and subsequent fractures[140, 141]. Despite a broad range of effective medications for osteoporosis being available in many countries, a ubiquitous care gap is evident for those that have suffered fragility fractures[142]. In response to this, IOF devoted the 2012 World Osteoporosis Day Report[143] to the Capture the Fracture Campaign[144], which aims to close the post-fracture care gap worldwide:

- If you are a postmenopausal woman who has suffered a fragility fracture, seek advice from your doctor on how to reduce your future fracture risk.
- If you are a health care professional, you should ensure that any patient aged 50 years or over who has suffered a fracture is assessed and treatment is considered. Visit *www.capturethefracture.org* to read about effective systems for secondary fracture prevention and consider implementing a Fracture Liaison Service in your locality.
- If you are a health care policy maker, visit *www.capturethefracture.org* to read about approaches taken in other countries to prioritise secondary fracture prevention initiatives in health care policy.

Postmenopausal women who have suffered a fragility fracture should seek advice from their doctors on how to reduce future fracture risk.

FAMILY HISTORY OF OSTEOPOROSIS AND FRACTURES

Genetics have considerable influence upon the peak bone mass attained by an individual[145-147] and, in the case of postmenopausal women, the rate of bone loss in the early years after menopause[51]. Heritability is evident as long as bone metabolism is primarily determined by physiological factors, such as hormonal levels and the activity of bone forming osteoblast cells. With advancing age, the impact of comorbid conditions, immobility, nutrition and absorption issues, and neurodegenerative disorders becomes dominant.

A parental history of fracture is associated with an increased risk of fracture that is independent of bone mineral density[148]. For women, the risk ratio is 1.17, 1.18 and 1.38 for any fracture, osteoporotic fracture and hip fracture, respectively.

MEDICATIONS

Glucocorticoid (GC) treatment is the most common cause of drug-induced osteoporosis. Glucocorticoid-induced osteoporosis (GIO) is primarily a disease of reduced bone formation affecting osteoblast cell function. However, GCs also prolong the life span of bone resorbing osteoclast cells and impair the function of osteocyte cells embedded in bone, which have been described as the 'orchestrator of bone remodelling' on account of the osteocyte's regulation of both osteoclast and osteoblast cell activity and additional function as an endocrine cell[149].

The effect of GCs on bone is rapid, with a significant proportion of bone loss occurring in the first 6 months of treatment. GCs effects are dose related so it is important that patients take the lowest effective dose for the shortest possible length of time. The prevalence of asymptomatic vertebral fractures among postmenopausal women receiving chronic GC therapy in an Italian study ranged from 30% for those aged under 60 years to 50% among those aged over 70 years[150]. These prevalence rates are considerably higher than those reported in the general

postmenopausal population, which ranged from 12-20% in the European Vertebral Osteoporosis Study[151].

Both anabolic (bone forming)[152] and anti-resorptive[153, 154] pharmacotherapies have been demonstrated to prevent GIO bone loss and fragility fractures. Adequate calcium and vitamin D are also essential adjunctive measures in the effective treatment of GIO. However, despite publication of professional guidelines on the need for bone prophylaxis in GC treated individuals[155,156], a significant care gap has been reported[157, 158]. Awareness of the risk that GC treatment presents to bone health must be increased amongst both patients and health care professionals.

DISEASES OF MALABSORPTION

Low bone mass is highly prevalent amongst sufferers of Crohn's disease[159,160] and celiac disease[161]. Many factors contribute to this association: in Crohn's disease these include intestinal resection and the resulting malabsorption of vitamin D and other nutrients, weight loss, chronic inflammation with increased levels of circulating cytokines, and frequent use of glucocorticoids. The major causes of osteoporosis amongst sufferers of malabsorption are malnutrition of calcium, vitamin D, protein and other nutrients, and the accompanying weight loss.

Professional guidelines on osteoporosis prevention and management in inflammatory bowel disease and celiac disease have been published[162].

RHEUMATOID ARTHRITIS

Sufferers of rheumatoid arthritis (RA) have lower BMD and are at increased risk of fracture[163, 164]. RA is the only secondary cause of osteoporosis in the FRAX® algorithm that is considered a predictor of fracture independent of bone density[165]. The degree of bone loss observed in RA is correlated with the severity of disease activity[166]. Proinflammatory cytokines released into the circulation from the inflamed synovium are thought to cause the bone loss.

EARLY MENOPAUSE

Premature menopause (before age 40 years) and early menopause (between ages 40 and 45 years) are associated with osteoporosis and a range of other health concerns[167]. The earlier the menopause occurs, the lower the bone density will be later in life[168]. Women who undergo oophorectomy (surgical removal of the ovaries) before age 45 years are at increased risk of developing osteoporosis. The loss of oestrogen triggers an increase in bone resorption and rapid bone loss (about 2-3% per year) which continues for about 5 to 8 years after menses cease. Thereafter, bone loss will slow to around 1% per year. Women who experience premature or early menopause should consider having a bone density scan conducted within 10 years of their menopause[168].

Medical treatments affecting bone health

Some medications may have side effects that directly weaken bone or increase the risk of fracture due to fall or trauma. Patients taking any of the following medications should consult with their doctor about increased risk to bone health:

- Glucocorticosteroids
- Certain immunosuppressants (calmodulin/calcineurin phosphatase inhibitors)
- Excess thyroid hormone treatment (L-Thyroxine)
- Certain steroid hormones (medroxyprogesterone acetate, luteinising hormone releasing hormone agonists)
- Aromatase inhibitors
- Certain antipsychotics
- Certain anticonvulsants
- Certain antiepileptic drugs
- Lithium
- Antacids
- Proton pump inhibitors

TAKE ACTION FOR A BREAK-FREE FUTURE

Menopause is a critical point in a woman's lifetime to discuss bone health with her primary care provider. Whilst the majority of fractures caused by osteoporosis occur in postmenopausal women[170-172] a significant awareness gap exists in this group. An IOF survey, conducted in 11 countries, showed denial of personal risk by postmenopausal women, lack of dialogue about osteoporosis with their doctor, and restricted access to diagnosis and treatment before the first fracture, resulting in under-diagnosis and under-treatment of the disease[173].

In view of these challenges, the previously described profound metabolic changes and anticipated acceleration in age-related bone loss with the menopause transition, it is essential that preventive measures be taken at menopause to optimize bone health. This includes specific recommendations for calcium and vitamin D supplementation, other supplements, exercise, need for bone density measurements, fracture risk assessment, and potential need for pharmacologic intervention and follow-up.

Good nutrition and an active lifestyle are essential to optimizing health in general, and musculoskeletal health in particular. They are the key foundations for osteoporosis prevention strategies in both genders, and across the lifecycle, but become particularly relevant with increased requirements for certain nutrients, after the menopause. The 2011 World Osteoporosis Day campaign message 'Embrace a bone healthy lifestyle' underscored the benefits derived from healthy nutrition, adequate vitamin D supplementation, and engaging in

Worldwide, at 50 years of age, 1 in 3 women will suffer a fracture in their remaining lifetime, and in women over 45 years of age, osteoporosis accounts for more days spent in hospital than many other diseases, including diabetes, myocardial infarction (heart attack) and breast cancer[169].

Questions patients should ask their doctor at a check up

- What are lifestyle changes I can implement at menopause to optimize bone health?
- What are recommendations for calcium, vitamin D and exercise?
- My mother had a hip fracture/or had a hump. What is my risk for fractures?
- Should I have a bone density test and how often should it be repeated?

physical activity to ensure stronger muscles and bones[174].

TOOLS TO ASSESS FRACTURE RISK

The WHO Fracture Risk Calculator - FRAX®

An individual's risk of developing chronic diseases, be it cardiovascular or cerebrovascular diseases or cancer is dependent on disease-specific risk factors, including lifestyle and clinical predictors, as well as family history. Osteoporosis and fragility fractures are no exception. Osteoporosis risk assessment is based on nutritional, other lifestyle variables, illness and medications, and family history, predictors that have been carefully described in the literature and reviewed in this report. In the last decade, tools to assess fracture risk have become available.

FRAX® – how it helps assess 10-year risk, and how to interpret the results[175]

FRAX® is a computer-based algorithm introduced in 2008 *(www.shef.ac.uk/FRAX)* which calculates the 10-year probability of a major fracture (hip, clinical spine, humerus or wrist fracture) and, individually, the 10-year probability of hip fracture[176]. This user friendly tool is designed to allow health care providers assess fracture risk at the individual level, target pharmacologic therapies to those at high risk, and thus prevent future fractures.

Fracture probability is computed taking both the risk of fracture and the risk of death into account. The algorithm had been constructed using information derived from the primary data of 9 population-based cohorts from around the world, including centres from North America, Europe, Asia and Australia, and was then validated in 11 independent cohorts with a similar geographic distribution with an excess of 1 million individuals[177].

Fracture risk is calculated from age, body mass index and dichotomized risk factors comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, alcohol consumption, ever use of long-term oral glucocorticoids, rheumatoid arthritis, and other causes of secondary osteoporosis. Secondary causes of osteoporosis are type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease[177]. Risk factors included in FRAX® were chosen to include only well-recognized, validated, and independent contributors to fracture risk while limiting their number and complexity[178]. Femoral neck BMD can be optionally input to enhance fracture risk prediction. The use of clinical risk factors in conjunction with BMD and age improves sensitivity of fracture prediction without adverse effects on specificity.

Since its launch in 2008, FRAX® has created a paradigm shift in care pathway models, and has become the cornerstone for the development of organization-based as well as national, osteoporosis guidelines[177,179-181]. In addition to its ease of use and wide availability on-line and through smart phones, FRAX® has added unique beneficial features compared to other risk calculators, including the fact that it takes into account country population-specific longevity rates as well as hip fracture incidence rates, thus providing risk estimates of direct relevance to the individual and allowing the development of country specific guidelines based on specific intervention thresholds[180, 182-186].

Today, FRAX® calculators are available for 51 countries which can be accessed online at *www.shef.ac.uk/FRAX*. Other models for countries without FRAX® will be developed, when sufficient data become available. In the absence of a FRAX® model for a particular country, a surrogate country should be chosen, preferably based on the likelihood that it is representative of the index country, and that best approximates the fracture risk of the index country.

As with all risk assessment tools, FRAX® is a tool which is complementary to clinical judgement when a physician decides to make a treatment decision. Clinicians should be aware of several limitations. The FRAX® assessment takes no account of dose responses for several risk factors such as smoking, steroid dose, presence of multiple fractures, and does not take some important risk factors into consideration, such as falls risk, markers of bone remodelling, and bone mineral measurements at other sites. These limitations acknowledged, FRAX® provides physicians and patients with an excellent basis on which to assess and discuss the individual's risk of future fracture.

FIGURE 5 The FRAX® on-line calculator and output[177].

OTHER FRACTURE RISK CALCULATORS

Other fracture risk calculators exist, such as QFracture®[187], the Garvan fracture risk calculator[188], but differ from FRAX® in their calculation of incidence rates rather than absolute probabilities. In FRAX®, fracture probability is computed taking both the risk of fracture and the risk of death into account. This is important because some of the risk factors affect the risk of death as well as the fracture risk. Examples include increasing age, sex, low body mass index (BMI), low BMD, use of glucocorticoids and smoking. FRAX® therefore combines clinical risk factors, BMD and country-specific mortality and fracture data, to calculate 10-year fracture probabilities in individual patients and provides a platform to assist clinicians and public health agencies in making rational treatment decisions based on treatment thresholds. FRAX® does not, however, define intervention thresholds, which depend on country-specific considerations, and vary from one country to another.

INTERVENTION THRESHOLDS BY NATIONAL ORGANIZATIONS

It is universally agreed that patients who suffer fragility fractures should undergo assessment for future fracture risk[26,140,143,144,180,182,189,207]. Most clinical guidelines and reimbursement criteria for specific osteoporosis medication support treatment of the majority of these fracture patients. However, targeting treatment is particularly important for other patients, including younger postmenopausal women, using FRAX®.

Country-specific FRAX®-based intervention thresholds, are usually developed targeting patients who do not suffer from severe osteoporosis or fragility fractures, and are based on any one of three paradigms:

- A fixed threshold that is independent of age, such as defined by the National Osteoporosis Foundation in the United States[182] and Osteoporosis Canada[180].
- An age-dependent increasing threshold, such as defined by National Osteoporosis Guideline Group (NOGG) in the United Kingdom[184] and by the Swiss Association against Osteoporosis in Switzerland[208]. The French also use a FRAX based age-dependent threshold, but only in subjects with a T-score > -3.0 at the spine, hip, or forearm[209].
- A hybrid model, such as developed for Lebanon, which uses a fixed threshold up to age 70 years, and an age dependent increasing threshold, modelled on the NOGG model, after age 70[186].

Illustrations of how fracture risk assessment features in several national guidelines follows.

United States: National Osteoporosis Foundation 2013 Clinician's Guide

The National Osteoporosis Foundation's treatment recommendations include[182]:

- Consider initiating pharmacologic treatment in those with hip or vertebral (clinical or asymptomatic) fractures.
- Consider initiating therapy in those with T-scores < -2.5 at the femoral neck, total hip or lumbar spine by dual-energy x-ray absorptiometry (DXA), after appropriate evaluation.
- Consider initiating treatment in postmenopausal women and men age 50 years or older with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck, total hip or lumbar spine by DXA and a 10-year hip fracture probability > 3% or a 10-year major osteoporosis-related fracture probability > 20% based on the U.S.-adapted WHO absolute fracture risk model (FRAX®; *www.NOF.org* and *www.shef.ac.uk/FRAX*).

Canada: 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis

The 2010 guidelines from the Scientific Advisory Council of Osteoporosis Canada highlight that management of osteoporosis should be guided by an assessment of the patient's absolute fracture risk based on a validated fracture prediction tool[180]. Specific recommendations include:

- Pharmacologic therapy should be offered to patients at high absolute risk (> 20% probability of a major osteoporotic fracture over 10 years).
- Individuals over age 50 years who have had a fragility fracture of the hip or vertebra and those who have had more than one fragility fracture are at high risk for future fractures, and such individuals should be offered pharmacologic therapy.
- For those at moderate risk of fracture, patient preference and additional risk factors should be used to guide pharmacologic therapy.

United Kingdom: National Osteoporosis Guidelines Group (NOGG)

The NOGG guideline treatment recommendations are summarised as follows[184]:

- Postmenopausal women with a prior fragility fracture should be considered for treatment without the need for further risk assessment, although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women.
- Assessment by the FRAX® tool should be undertaken in all postmenopausal women without fracture but with a WHO risk factor or a BMI < 19kg/m².

Following the assessment of fracture risk obtained by entering risk factors only into FRAX®, the patient may be classified to be at low, intermediate or high risk.

- **LOW RISK** Reassure and reassess in 5 years or less depending on the clinical context.
- **INTERMEDIATE RISK** Measure BMD and recalculate the fracture risk to determine whether an individual's risk lies above or below the intervention threshold.

- **HIGH RISK** Can be considered for treatment without the need for BMD, although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women.

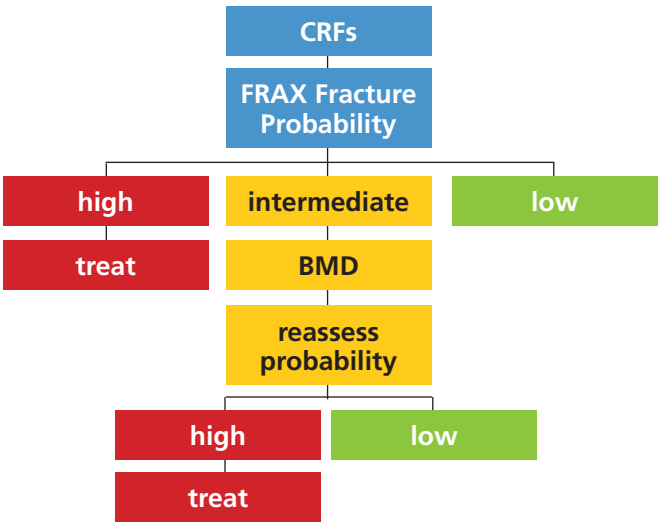
The intervention threshold is age specific, and is set at a risk equivalent to that of a women with an equivalent age and a history of prior fracture, as calculated by FRAX®, and therefore rises with age. As fracture risk rises markedly with increasing age, the proportion of women in the UK potentially eligible for treatment rises from 20-40% with age.

INDICATIONS FOR BONE MINERAL DENSITY TEST

Numerous national[180,182,184], regional and local guidelines are available which describe indications for BMD testing, many with an overlap in some but not all indications, and are captured by the recommendations provided by the International Society for Clinical Densitometry (see *http://www.iscd.org/*). The key indications for BMD testing amongst postmenopausal women are:

- Previous fragility fracture
- Family history of osteoporosis and/or fragility fracture

FIGURE 6 The UK NOGG guideline algorithm[210].



- Use of certain medications, particularly:
  - Glucocorticoids
  - Aromatase inhibitors
- Diseases of malabsorption, primarily:
  - Crohn's disease
  - Celiac disease
- Rheumatoid Arthritis
- Early menopause, either:
  - Premature (under age 40 years)
  - Early (40 to 45 years)

BONE MINERAL DENSITY TESTING IS A SIMPLE AND NONINVASIVE PROCEDURE.

PHARMACOLOGIC MANAGEMENT OF OSTEOPOROSIS

The cornerstone of preventive strategies for all patients regardless of risk include lifestyle interventions: weight-bearing, balance and strengthening exercises, smoking cessation, and optimization of total calcium and vitamin D intake. For patients at risk of falls, advice on fall-prevention should be provided. Drug therapies are needed in addition for patients at high risk for fractures, as defined by the NOF[182], NOGG[184] and Osteoporosis Canada guidelines[180], or those of another appropriate national organization. Although the major pivotal trials for established drug therapies randomized patients with low bone density and/or fragility fractures, none of them randomized subjects based on actual fracture risk assessment. However, post-hoc analyses revealed that a high FRAX®, in some trials, was able to identify subjects who would benefit most from pharmacologic intervention[211-214].

Several recent reviews detailed the anti-fracture efficacy of approved treatments for postmenopausal women with osteoporosis when given with calcium and vitamin D (*see table 4*)[215-220].

Details of the therapies licensed for the treatment of osteoporosis throughout the world follow (in alphabetical order):

Bisphosphonates Represent the cornerstone therapeutic modality for osteoporosis. These analogues of naturally occurring pyrophosphate can be administered orally in weekly or monthly regimens (alendronate, risedronate, and ibandronate) or intravenously every three months (ibandronate) or yearly (zoledronate)[179,218,221,222]. The anti-resorptive action of bisphosphonates persists following discontinuation of therapy. Potential concerns regarding long term use of bisphosphonates have stemmed from associations with rare but serious adverse events, including atypical sub-trochanteric fractures and osteonecrosis of the jaw. This has led to re-consideration of optimal treatment duration and the importance of drug holidays[218, 221]. These agents are widely available, affordable, and in view of their established efficacy and limited toxicity profile, are considered as the first line therapeutic option for many patients[179, 215, 216, 219, 222].

Denosumab A very potent anti-resorptive compound, a humanized monoclonal antibody against RANKL, a member of the tumor necrosis factor superfamily of compounds, agents that are essential for bone resorption. Denosumab is administered subcutaneously twice a year, and in contrast to bisphosphonates its anti-resorptive effect subsides upon its discontinuation, which may be an advantage or disadvantage depending on whether viewed from the point of view of reducing side effects, or persisting efficacy. Both osteonecrosis of the jaw and atypical subtrochanteric fracture have now been described in denosumab treated patients, but similar to bisphosphonates, the occurrence of the former is more common when used in patients suffering from cancer rather than osteoporosis. The efficacy of denosumab is significant for protection against vertebral, non-vertebral and hip fractures, and it compares very favorably against other anti-resorptive medications. Due to its relatively recent release, the long term safety of denosumab based on post-marketing experience remains to be established.

Hormone Replacement Therapy In the Women's Health Initiative trials hormone replacement therapy (HRT) was shown to reduce hip and non-vertebral fractures in older postmenopausal women, mean age 65 years[223, 224]. This was, however, at the expense of an increased risk for several adverse outcomes. These include cardiovascular disease, cerebrovascular disorders, and breast cancer, in the trial using oestrogen (Premarin®) combined with progesterone (medroxy-progesterone acetate), and

TABLE 4 Anti-fracture efficacy of the most frequently used treatments for postmenopausal osteoporosis when given with Calcium and Vitamin D as derived from controlled trials[215].

	Effect on vertebral fracture risk		Effect on non-vertebral fracture risk	
	osteoporosis	established osteoporosis[a]	osteoporosis	established osteoporosis[a]
Alendronate	+	+	n/a	+ (including hip)
Risedronate	+	+	n/a	+ (including hip)
Ibandronate	n/a	+	n/a	+[b]
Zoledronic acid	+	+	n/a	+[c]
HRT	+	+	+	+ (including hip)
Raloxifene	+	+	n/a	n/a
Teriparatide and PTH	n/a	+	n/a	+[d]
Strontium ranelate	+	+	+ (including hip[b])	+ (including hip[b])
Denosumab	+	+[c]	+ (including hip)	+[C]

n/a no evidence available
+ effective drug
[a] women with a prior vertebral fracture
[b] in subsets of patients only (post hoc analysis)
[c] mixed group of patients with or without prevalent vertebral fractures
[d] shown for teriparatide only

mostly cerebrovascular diseases in the trial using oestrogen (Premarin®) alone, in women who underwent a hysterectomy[223, 224]. It is therefore not an optimal treatment choice in older postmenopausal women. However, short term use of HRT remains an option in a younger women with menopausal symptoms and no contra-indications to its use. Two trials, ELITE (Link) and KRONOS[225,226], will provide some insight into the safety and efficacy of HRT in younger postmenopausal women.

Raloxifene A tissue selective oestrogen receptor modulator (SERM) that is used for the prevention and treatment of osteoporosis. Raloxifene reduces the risk of vertebral fractures, but not hip fractures, and has the added advantage of reducing the risk of breast cancer, without any adverse effect on the endometrium. It does not seem to affect the risk of cardiovascular disorders, but, similar to HRT, increases the risk of venous thromboembolism. It provides a good therapeutic option in late postmenopausal women at high risk for vertebral but not hip fractures and with concerns regarding breast cancer risk.

Strontium ranelate An orally active drug, strontium ranelate is most effective in reducing the risk of vertebral fractures and to a lesser extent non-vertebral fractures. It is approved in Europe by the European Medicines Agency (EMA) for the treatment of osteoporosis, but is not available in the USA. Post-marketing surveillance studies revealed the possibility of severe skin reactions, therefore it should be discontinued permanently if a skin reaction develops. Recent guidance from the EMA, as a result of trial and surveillance data, has advised that strontium ranelate should not be used in those with high cardiovascular risk or where there is a high risk of thromboembolic disease. Other strontium compounds, often marketed over the internet, have not been demonstrated to be effective and should not be used to treat osteoporosis.

Teriparatide Subcutaneous administration of parathyroid hormone results in an anabolic (bone forming) action at multiple skeletal sites. While the sequential use with a subsequent anti-resorptive agent is essential to prevent the significant bone loss noted after its discontinuation, concomitant administration with bisphosphonates does not provide any added benefit. The occurrence of osteosarcoma in rats, when used at doses several fold higher than those administered in humans, has led regulatory agencies to limit its use to two years, but post-marketing surveillance did not reveal any concerns in humans. Teriparatide has been shown to reduce the risk of vertebral and non-vertebral fractures, but not of hip fractures, and its use is indicated in subjects with severe osteoporosis, and/or multiple vertebral fractures[215, 217].

The overall safety profile for the above therapies is favorable. Cost implications differ, generic bisphosphonates being the most affordable, followed by SERMS, branded bisphosphonates, and then denosumab and teriparatide, with some variations depending on the specific country. The ultimate selection of a specific pharmacologic treatment should take into account the patient's individual risk profile including the risk for a specific type of fractures (spine versus hip), co-morbid conditions, poly-pharmacy, and patient's preference. Finally, cost and cost-effectiveness considerations, insurance plans, and national health policies, will undoubtedly also modulate choice of therapeutic options.

PATIENTS AT HIGH RISK OF FRACTURE SHOULD DISCUSS LIFESTYLE INTERVENTIONS AND DRUG TREATMENT OPTIONS WITH THEIR DOCTORS.

IMPORTANCE OF ADHERING TO TREATMENT

Like all medicines, osteoporosis treatments can only work if they are taken properly. As reported for other chronic diseases[227-231], up to half of osteoporosis sufferers stop their treatment after only one year[232]. The primary reasons why individuals should adhere to treatment are:

- Larger increases in BMD will be achieved[233].
- The amount of bone lost through the resorption process will be reduced[234].
- Reduction of fracture risk is greater[235].

Eight tips to give patients to help them remain on treatment

1. Think about ways to take your medication (e.g. first thing in the morning before breakfast) in order to minimise the impact on your everyday life.
2. If you take regular pills for your osteoporosis, try to take your treatment at the same time each day, week or month.
3. Use a diary to remind yourself to take your medication and collect your prescription, or put a reminder somewhere you will see it frequently.
4. Make a note of the specific actions you need to remember when taking your treatment and keep this somewhere memorable.
5. Be prepared and plan for changes in your routine that will make it more difficult for you to take your medication, such as holidays or special events.
6. Ask your family and friends to support you to stay on treatment. Tell them about your medication and explain to them why it is important for you to continue to take it.
7. Speak to your health professional about difficulties you are experiencing. They will be able to give you advice on managing your osteoporosis medication and may be able to suggest other treatment options.
8. Contact your local patient society; they can offer you support and put you in touch with other people who are in a similar situation. You can also communication with people who have osteoporosis on the OsteoLink social network site **www.osteolink.org**.

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Bone loss accelerates at menopause, making women over 50 particularly susceptible to the potentially devastating effects of osteoporosis and fractures. No matter what your age, strategies for prevention should include a combination of targeted exercise, bone-healthy nutrition, avoidance of negative lifestyle factors, and early identification of individual risk factors. Take action today to maintain strong bones and muscles that will carry you through a lifetime.

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