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Lowell T. Duncan
Editor

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Contents

Preface

This volume includes eight chapters that detail recent advances in health and disease. Chapter One discusses the risk factors and management strategies of fragility fractures. Chapter Two summarizes how cognitive reserve can protect humans from normal aging processes and the appearance of neuropathological diseases. Chapter Three gives an overview of the fracture healing process.

Chapter Four provides new insights into discovering new drugs against inflammation through computational methods. Chapter Five details the correlation between ant resorption therapies in osteoporosis and the development of atypical femoral fractures. Chapter Six explains the health damage caused by the major metabolite of nicotine, cotinine.

Chapter Seven proposes a fast, non-invasive method for the analysis of virus genomes in warts and their destruction by hypoxia. Lastly, Chapter Eight aims to assess the magnitude of throat carriage, associated factors, and antimicrobial susceptibility patterns of Group A Streptococus among healthy school children in Eastern Ethiopia.

Chapter 1

Fragility Fractures: Risk Factors and Management Strategies

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Abstract

Fragility fractures are pathological fractures that occur after minimal trauma on bones whose structural integrity and strength have been

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diminished by an underlying disease process. They mostly affect the elderly and can cause serious and long-term morbidity, reduce quality of life and increase mortality. Each fracture increases the risk of another fracture by 2 to 5 times, with the result that the annual incidence of fragility fractures exceeds the combined annual incidence of heart attack, stroke and breast cancer. It is estimated that after such a fracture, only half of patients will return to their previous level of activity, and depression, chronic pain and disability are common problems.

Fragility fractures are in fact both a sign and a symptom of underlying osteoporosis either primary or secondary. Osteoporosis silently contributes to the reduction of bone density and deterioration of microarchitecture, causing bones to become "brittle" and subject to fracture even after low-energy accidents, such as a simple fall. Primary osteoporosis can come as a natural consequence to aging or as a result of the absence of oestrogens while secondary osteoporosis can present as a complication of other disease that affect bone metabolism. Several parameters have been shown to independently contribute to osteoporosis and frail skeleton and are usually categorized to modifiable or non-modifiable risk factors. These factors can be targeted by healthcare models to identify the population at risk and focus on prevention strategies which can play a vital role in reducing the incidence of what seems to have reached epidemic proportions.

Patients with fragility fractures are the most commonly treated orthopedic trauma patients, occurring in large numbers in every general hospital in every country. The aging of society is causing a huge increase in the incidence of fragility fractures and brings an unbearable burden to patients, families in health systems and societies worldwide. Proper management should focus on treating the fracture at the right time, the right structure and by the appropriate health professionals, but also promote prevention measures that can impact on modifiable risk factors. If a first fragility fracture is recognized and osteoporosis treated, the risk of a future fracture can be reduced by approximately 50%, preventing the downward spiral in health and quality of life that often follows fragility fractures. Prevention can be achieved by changing lifestyle factors, such as nutrition and exercise, as well as pharmacological intervention to restore bone strength, and by preventing falls.

Keywords: fragility fractures, osteoporosis, management, quality of life

Overview

Fragility fractures (FFs) are commonly defined as any fracture in an adult over age 50 that occurs as a result of the application of mechanical forces that would not ordinarily lead to a fracture (J A Kanis, Oden, et al. 2001). Normal bones

in healthy individuals should be able to withstand this amount of low-energy trauma without sustaining a fracture. The most common low-energy trauma setting leading to a FF is a fall from standing height in the elderly population, but FFs may also be defined as pathological fractures that result from minimal or no identifiable trauma at all, suggesting in all cases weakness of the skeleton (Sànchez-Riera and Wilson 2017). Fractures occurring before the age of 40 are not considered FFs (A Papaioannou et al. 2010). In this respect, a stress fracture, as may occur in runners for example, is a clinical entity that, though sharing similarities, should not be confused with FFs (Acevedo et al. 2018). While stress fractures also come as a result of the application of low force, the forces are in this case repetitive, usually consisting of many thousands of cycles, to the point of normal bone failure (Migliorini et al. 2021).

Despite the fact that almost any bone can sustain a FF, there are three anatomical sites identified as typical FFs locations: the vertebrae (lumbosacral spine), the hip (proximal femur), and the wrist (distal radius) (A Papaioannou et al. 2010). Other sites commonly affected include the pelvis, the ribs, and the arm and shoulder (proximal humerus) region. FFs are pathological fractures that occur after minimal trauma on bones whose structural integrity and strength have been diminished by an underlying disease process. FFs are in fact both a sign and a symptom of underlying osteoporosis, either primary or secondary, which silently contributes to the reduction of bone density and deterioration of microarchitecture. Osteoporotic fractures are associated with low bone mineral density (BMD) and microarchitectural defects and occur more frequently than heart attacks, strokes, and breast cancer combined (Seidman et al. 1985; Cummings 1989). Several parameters have been shown to independently contribute to osteoporosis and frail skeleton, the identification of which plays a vital role in prevention strategies employed by novel healthcare models in an attempt to fight back what seems to have reached epidemic proportions (Johnell and Kanis 2006).

Elderly patients with FFs are the most commonly treated orthopedic trauma patients, with one fracture occurring globally every three seconds (Hernlund et al. 2013). This type of fracture is associated with high human and socio-economic impact, morbidity, and mortality and combined with the aging of society, brings an unbearable burden to patients, families, health systems, and societies worldwide (Center et al. 2007; Borhan et al. 2019). For individuals in specific, FFs frequently result in loss of autonomy, deterioration in the quality of life, and need for care (N. D. Nguyen et al. 2007). Strategies are continually being developed and refined both to prevent these fractures and to manage them when they occur (Singer et al. 2015).

Epidemiology

As already mentioned, FFs are common in older people and occur most frequently in the thoracolumbar spine (vertebrae), proximal femur (hip), and distal radius (wrist), amongst practically any bone or anatomical location (Sànchez-Riera et al. 2010). Concerning the age- and gender-specific fracture incidence for each of the different sites, it was recorded a strong age-related increase in incidence excluding the locations of the proximal forearm, tibia, fibula, ankle, and foot (Bergh et al. 2020). This finding indicates that low BMD does not influence fracture incidence rates at some anatomical sites (Amin et al. 2014).

The total number of incidental FFs was estimated to be nine million annually worldwide in 2000, of which 1.6 million involved the hip, 1.7 million the forearm, and 1.4 million were clinical vertebral fractures (Johnell and Kanis 2006). These numbers exceed the combined annual incidence of stroke, myocardial infarction, and breast cancer, and are expected to significantly increase by 2025 (Leibson et al. 2002; Borhan et al. 2019). There were estimated to be 2.7 million new FFs in the largest five countries of the European Union plus Sweden (EU6) in 2017, equivalent to 7,332 fractures per day (or 305 per hour) (Borgström et al. 2020). Almost twice as many fractures occurred in females (66%) compared to males (Borgström et al. 2020). Hip, vertebral and distal forearm/proximal humerus fractures accounted for 19.6%, 15.5%, and 17.9% of all fractures respectively, whereas other FFs accounted for 49% of the fracture burden (Borgström et al. 2020).

The number of new FFs in 2017 by country, showed that Germany had the highest number in both males and females-approximately 765,000 incident fractures in total, predominately reflecting the large population size and comparatively high fracture incidence (Borgström et al. 2020). When fracture numbers were expressed as a rate of the population at risk, there was a greater than two-fold range in risk that varied from 15/1000 in France to 32/1000 in Sweden (Borgström et al. 2020). Currently, in the UK, approximately 549,000 new FFs occur each year, including 105,000 hip fractures, 86,000 vertebral fractures, and 358,000 other fractures (i.e., fractures of the pelvis, ribs, humerus, forearm, tibia, fibula, clavicle, scapula, sternum, and other femoral fractures), of which 33% are sustained by males (Scotland 2019; Borgström et al. 2020). In Canada, studies have shown a sharp increase in the number of hip fractures between 1981 and 1995, from 17,823 to 27,375 respectively, and their number is projected to reach 88,124 fractures by the year 2041 (Ioannidis et al. 2009).

A Brazilian Osteoporosis Study (BRAZOS), the first epidemiological study carried out in a representative sample of Brazilian males and females aged 40 years or older, showed that the prevalence of FFs was about 15.1% in females and 12.8% in males (Pinheiro et al. 2008). Females are more affected than males, as they have a higher incidence of osteoporosis. More than one in three females and one in five males will have one or more osteoporotic fractures during their lifetime (National Osteoporosis Guide Line Group (NOGG) 2017), Setting the lower age threshold to 50 years, results are not affected for men, with 20% FF incidence for the remaining years of life, while in women the risk rises to 50% (van Staa et al. 2001). Osteoporosis usually affects frail individuals, increasing the risk of fracture for the remaining lifetime (van Staa et al. 2001; G. Li et al. 2017). The lifetime risk of osteoporotic fractures lies within the range of 40-50% in females and 13-22% for males, with mortality higher in males (Olszynski et al. 2004). Patients aged 65 years and above, suffer fragility status and increased risk of adverse health outcomes such as impaired mobility, prolonged hospitalization, residual disability, and reduced life expectancy (Migliorini et al. 2021).

An incident FF is associated with an acute risk of a subsequent fracture occurring within one-two years, known as an imminent fracture risk (Johansson et al. 2016). When examining a 10-year period after an incident fracture, it was reported that the majority of subsequent FFs tend to occur within the initial two years (Roux and Briot 2017). Sixty-one percent of subsequent fractures were reported to occur within the initial two years after a hip fracture, 54% after a forearm fracture, and 53% after a humerus fracture (J. A. Kanis et al. 2020), Studies have shown that a FF occurring at any site within one-two years prior, including non-vertebral sites such as wrist and humerus (proximal or undefined anatomical location), was a better predictor of subsequent fracture risk than a more temporally distant fracture (Balasubramanian et al. 2018; Huntjens et al. 2010; Maravic, Briot, and Roux 2014; Clinton et al. 2009). If a first FF is recognized and underlying osteoporosis treated, the risk of a future fracture can be reduced by approximately 50%, preventing the downward spiral in health and quality of life that often follows, particularly after a hip fracture (Bukata et al. 2011). In addition to the increased risk of subsequent fracture and increased mortality, survivors after an initial fracture also demonstrate an increased dependence and reduced quality of life (Amarilla-Donoso et al. 2020).

Vertebral fractures are the most common manifestation of osteoporosis, and the most common single osteoporotic fractures worldwide, occurring in 30–50% of people more than the age of 50 (Ballane et al. 2017). In contrast to

hip fractures, many factors limit the availability of reliable information on their epidemiology: two-thirds to three-fourths of vertebral fractures are clinically silent, and less than 10% require hospital admission, which itself may vary due to geographic differences in access to healthcare (Veronese, Kolk, and Maggi 2020). Epidemiological data suggested that the vertebral compression fractures incidence was approximately 10 times higher than that of femoral fractures, with an estimated 1-1.5 million cases (about 1% of the entire population) per year in Japan (Orimo et al. 2000; 2009). The incidence of symptomatic patients with vertebral compression fractures requesting medical treatment at Sado Island was recorded as 1,100 per 100,000 per year among females at the age of 70 years (Sakuma et al. 2008). Symptomatic vertebral fractures were estimated to constitute approximately to 25% of all cases in females at the age of 70 in Japan (Sakuma et al. 2008). In Sweden, it was reported that 15% of 3014 community-living men aged 69-81 years had at least one vertebral fracture and that only 10% of them were aware of their fractures (Kherad et al. 2015). In Europe, studies in males and females over 50 years of age reported that the incidence of clinical vertebral fracture was higher in males than in females under 55 years, but the risk was increasing in females after the age of 60 years (Kristine E Ensrud and Schousboe 2011). In terms of prevalence data, it is estimated that, in both males and females, prevalence linearly increases with age independently of country, with some data suggesting that almost half of the very old people (i.e., over 85 years of age) are affected by a vertebral fracture (K E Ensrud 2013).

Proximal femoral fractures, commonly described as hip fractures, represent the most serious injury of the frail skeleton amongst FFs (Bukata et al. 2011). The mean age of the patients affected is about 80 years, and over 75% of those fractures occur in both genders over 75 years of age (Hernlund et al. 2013). Epidemiological studies have shown that the incidence of proximal femoral fractures increases gradually with age, starting at 40 years, with an abrupt increase after 75 years of age (Hernlund et al. 2013). Indeed, hip fractures are rare at the age of 50 years but become the predominant osteoporotic fracture after the age of 75 years.

The typical profile of the patients affected involves females, showing low BMD, and following a less active lifestyle (Kelsey et al. 1992). The incidence in females was determined to increase 44-fold between the ages of 55 and 85, and the relative risk contribution of aging on the proximal femoral fractures was 11-fold greater than that of reduced BMD (Jarvinen et al. 2015; J A Kanis et al. 2000; Marshall, Johnell, and Wedel 1996). Most injuries result from indoor incidents, and more than 85% of those fractures occur by falls, as the

number of falls is another risk factor (Kelsey et al. 1992; Marshall, Johnell, and Wedel 1996). The incidence of falls was significantly higher among individuals over the age of 75 years than among those younger than 74 years, which was similar to the incidence of proximal femoral fractures (Rubenstein 2006).

Hip fractures nearly always require hospitalization and are fatal in almost a quarter of all cases (Bukata et al. 2011). Previous data suggested that hip fractures are fatal in 20% of the cases and permanently disable 50% of those affected, while only 30% of the patients fully recover (Ioannidis et al. 2009). National Osteoporosis Guideline Group (NOGG) also confirmed that following a hip fracture, about half of those admitted can no longer live independently on discharge from the hospital, and 20% die within a year (National Osteoporosis Guide Line Group (NOGG) 2017). Similar research in the American population confirmed that there is a significant increase in morbidity and mortality in elderly patients who sustain hip fractures (Brauer 2009). A 25% to 30% mortality rate in the first year following a hip fracture was revealed, whereas in those who survive, more than half do not return to their pre-injury level of function, and one in four patients rely on long-term nursing home care (Jennings et al. 2010).

Wrist fractures, a term commonly used to describe distal radius fractures, are the third most common type of osteoporotic fracture, accounting for up to 18% of all fractures among the elderly (Thompson, Taylor, and Dawson 2004). However, their impact on quality of life due to post-fracture complications and impaired function is often underestimated (Vergara et al. 2016; González et al. 2014). These distal forearm fractures are often ‘the first’ FF, followed by a subsequent hip or vertebral fracture (Crandall et al. 2015; Johnson et al. 2017).

The most common distal forearm fracture is the so-called Colles’ fracture, and the median age for female patients sustaining the injury is around 65 years of age (Nellans, Kowalski, and Chung 2012). Wrist fractures occur at a relatively young age, and their incidence was not found to increase in the elderly suggesting that osteoporosis may not be a major contributor, even though distal radius is one of the most common sites of upper limb fractures in the elderly (Hagino et al. 1999). In females, the incidence has been found to increase in their late 50s, reaching 300-400 per 100,000 individuals per year between 60 to 70 years of age, however, it does not increase in their 80s and actually tends to decrease after the age of 85 years (Kelsey et al. 1992). In males, the incidence of wrist fractures was found to be 1.6 per 1,000 person-

years overall, ranging from 1.0 among men aged 65-69 to 2.4 among men aged over 80 years (N. C. Wright et al. 2018).

FFs also have a major economic impact. In the UK, osteoporosis causes over 200,000 fractures per year, costing the NHS over £ 1.7 Billion (National Osteoporosis Guide Line Group (NOGG) 2017). Direct medical costs from FFs to the UK healthcare economy were estimated at £1.8 billion in 2000, with the potential to increase to £2.2 billion by 2025, and with most of these costs relating to hip fracture care (R. T. Burge et al. 2001). For the year 2017, the costs of FFs to the NHS exceeded £4.7 billion per annum, of which £2.6 billion is directly incurred after an incident fracture (£1.1 billion for hip fractures alone), with more than £1.7 billion attributable to institutional care costs post-fracture (Leal et al. 2016). Total direct costs for 2019 were £5.4 billion accounting for 2.4% of healthcare spending (John A Kanis et al. 2021). In Sweden, the total cost of FFs is about 3.2% of the total healthcare cost [60]. The direct cost of treating osteoporosis in Canada is estimated at $1.3 billion annually (Lorrain et al. 2003). In 2005, more than two million osteoporosis-related fractures in the United States, with 71% occurring in females and 29% in males, had a total cost of nearly $17 billion (R. Burge et al. 2007). By 2025, fractures and associated costs are predicted to grow by more than 48% (R. Burge et al. 2007).

The burden of FFs is expected to grow with the aging of the population, as it is particularly high in adults aged over 65 years (Alexandra Papaioannou et al. 2010; Odén et al. 2015). In Canada, the predicted increase in the number of older adults from 15% of the population in 2011 to 25% of the population in 2031, is expected to result in a proportional increase in the number of FFs in the next decades (Statistics Canada's National Contact Centre 2010). The National Osteoporosis Guideline Group (NOGG) estimates that, due to the aging of the population, if changes are not made in current practice, there will be a doubling of osteoporotic fractures over the next 50 years (National Osteoporosis Guide Line Group (NOGG) 2017).

Moreover, it has been estimated that during the period from 2011 to 2026, 78 million individuals will reach 65 years of age in the United States alone, and during the 20-year period from 2010 to 2030, it is expected that the United States will see a rise in the elderly population significantly higher than that of the prior 20 years or of the following 20 years (Browner et al. 2019). In the United States, by 2025, the annual incidence and costs of fragility fractures is projected to increase by 50% (K E Ensrud 2013). Similarly, aging of the UK population is predicted to give rise to a 19.6% increase in the number of FFs by 2030 if changes are not made to current practice (Borgström et al. 2020).

Risk Factors

FFs are pathological fractures that occur after minimal trauma on bones whose structural integrity and strength have been diminished by an underlying disease process. Such fractures are caused by weakness of the bone structure that leads to decreased mechanical resistance to normal mechanical loads. The mentioned process is most commonly due to osteoporosis, but may also be due to other pathological conditions such as infection, inherited bone disorders, bone cysts, osteomalacia, Paget's disease, osteitis, benign bone tumors, primary or secondary malignant bone tumors, and metastasis (Salehi et al. 2019).

Lifestyle factors may also contribute to increased risk of FFs including lack of regular exercise, sedentary lifestyle, poor quality of life, and reduction of mobility (Loh et al. 2008; Adami et al. 2011; Pinheiro et al. 2008). Additional non-BMD factors that also influence fracture risk include current smoking, low body mass (<20 kg/m2), low body weight, and anorexia nervosa (J A Kanis et al. 2013; Chaplin 2021).

Osteoporosis

Osteoporosis is the most common bone disease in humans and a major risk factor for FFs (International Osteoporosis Foundation 2018). It silently contributes to the reduction of bone density and deterioration of microarchitecture, causing bones to become "brittle" and subject to fracture even after low-energy accidents, such as a simple fall (International Osteoporosis Foundation 2018). Since bones become more porous and fragile with age, the disease is mainly found in the older population and is more common among females than males.

There are two primary forms of osteoporosis. Postmenopausal osteoporosis (type I) affects women after menopause due to an abrupt decline in estrogen production followed by increased osteoclast activity and trabecular bone loss (Ji and Yu 2015). Type II osteoporosis, also known as senile osteoporosis, appears with advancing age in both men and women due to a disruption in the balance of bone formation and absorption and is characterized by both trabecular and cortical bone loss (Sözen, Özışık, and Başaran 2017). Secondary forms of osteoporosis are associated with a vast range of diseases and drugs (Adami et al. 2011). Osteoporosis is a common

underlying factor that contributes to the development of fractures in frail individuals, as it impairs BMD with profound micro-architectural deterioration of the bone which leads to increased fragility (Rachner, Khosla, and Hofbauer 2011).

Worldwide, osteoporosis causes more than nine million fractures a year, meaning there is an osteoporotic fracture happening every three seconds (Trajanoska and Rivadeneira 2019). Those who suffered an osteoporotic fracture have a higher risk for further fractures (Compston, McClung, and Leslie 2019). Overall, more than 60% of pelvic ring fractures in the elderly are associated with osteoporosis (Soles and Ferguson 2012). After the age of 50 years, most sites of fracture can be considered characteristic of osteoporosis. As already mentioned, fractures at the hip and vertebrae locations are among the most common and serious sites of osteoporotic fracture. FFs of the humerus, forearm, ribs, tibia (in females, but not including ankle fractures), pelvis, and other femoral fractures after the age of 50 years are fractures associated with low BMD (Warriner et al. 2011). There are relatively few studies that have evaluated the risk factors for osteoporotic fractures in males and these have primarily been in Caucasians (J. Kanis et al. 1999; T. v Nguyen et al. 2001).

Reduced BMD

Osteoporosis is defined by reduced BMD, which is a major risk factor for FFs, whereas low BMD is widely used as a diagnostic indicator for osteoporosis (Ahlborg et al. 2003; LaFleur et al. 2008). Low BMD, one of the most important indicators of fracture risk, is both a fixed and modifiable risk factor determined by a wide range of factors, including family history, age, and lifestyle (Zhou et al. 2017). It has been demonstrated that the reduction of a single standard deviation in BMD corresponds to an increase in fracture risk of 1.5 to 3-fold (Adami et al. 2011). However, fracture risk is not only related to BMD, and in this respect, T-score values alone are not sufficient to define the probability of fracture and determine when a patient needs to be treated (J A Kanis, Johnell, et al. 2001). Moreover, the majority of fractures occur in patients presenting with osteopenia (T-scores of -2.5 to -1.0) (Miller et al. 2004). Low BMD at age 48 is also an independent predictor for FFs (Ola Svejme et al. 2013).

Advancing Age

Age is one of the most significant factors contributing to an increased risk of fracture regardless of BMD, reflecting not only skeletal strength impairment due to bone aging, but also the negative effects of the comorbidities found in elderly patients (J A Kanis, Johnell, et al. 2001; Burger et al. 1998). Age contributes, independently of BMD, to fracture risk, therefore, in the presence of the same BMD score, the risk of fracture will be higher for the elderly than for the young (Chaplin 2021). As the risk of fracture increases with age and average life expectancy around the world rises, more individuals are expected to sustain FFs (JA. 2002; John A Kanis et al. 2005).

Another major problem regarding the elderly is their reduced muscular functionality. This is an age-related condition, but it is often exaggerated by deficient nutrition and reduced mobility (Saadeh et al. 2021). Weakness is one of the five elements that define frailty syndrome (Fried et al. 2001). Moreover, the 'frail phenotype' is associated with a very high risk of falls leading to fracture (Tom et al. 2013). Because of increased bone loss after the menopause in females, and age-related bone loss in both females and males, the prevalence of osteoporosis increases markedly with age, from 2% at 50 years to more than 25% at 80 years in females (Berger et al. 2008; The North American Menopause Society 2021). As the longevity of the population increases, so will the incidence of osteoporosis and FFs, as already mentioned (British Orthopaedic Association 2007). Patients aged 50 years and older who recently sustained a FF are at increased risk of subsequent fractures (van Helden et al. 2005; Huntjens et al. 2010). The peak incidence of osteoporotic pelvic fractures is in the 9th decade of life (Küper et al. 2019).

Falls

An additional age-related factor that plays a fundamental role in FFs lies in falls. Falls account for one of the most common and serious issues contributing to a disability and are extremely common in the frail population, but their possibility is usually underestimated (Abdelrahman et al. 2018). Falls in the elderly dramatically impact life expectancy, as the associated complications are often severe, and the recovery process is prolonged and difficult to complete (Corso et al. 2006). In addition to the parameters used to monitor the specific risk of falling, a previous fall also significantly impacts the patient's functional decline (Ferrucci et al. 2004). Falling has a high incidence rate in

the elderly population nowadays and it has become a public health problem attracting great concern (Järvinen et al. 2008). More than 30% of individuals who are at the age of 65 and over fall every year and almost half of the incidents consist of recurrent falls (Appeadu and Bordoni 2022). Over the age of 80, studies show that 40-50% of the population living in the community fall at least once a year and that 90% of FFs in patients with osteoporosis are caused by falls (Park et al. 2019; Barrett-Connor et al. 2009). Recurrent and previous falls are also a serious problem for the elderly population and are an independent risk factor of FFs (Yoh 2006).

Fall-related risk factors add significantly to fracture risk and often overlap with risk factors for osteoporosis (Dionyssiotis 2012). Age and history of falls are key risk factors among many, including muscle weakness, balance disorders, visual impairment, and dementia (Tsuda 2017). In the case of dementia in particular, a condition affecting 47.2% of individuals over 85 years of age, studies report an 8-fold higher risk of falling compared to those without dementia (Friedman et al. 2010).

Vitamin D

Vitamin D's (Vit.D) multifactorial role in bone and muscle health has been historically associated with fracture risk and several studies have examined the role of supplementation of Vit.D in preventing FFs (Lips et al. 1996; Holick 2006; Kong et al. 2022). Vit.D deficiency hampers bone mineralization with a negative effect on bone strength while promoting muscle weakness and increases the risk of sarcopenia (Q. Wang et al. 2020). However, studies on the correlation between low serum Vit.D and the risk of FFs have produced mixed results (Barbour et al. 2012; Looker and Mussolino 2008; Holvik et al. 2013; Ginsberg et al. 2018; Zhang et al. 2019).

Recent evidence supports a U-shaped effect of vitamin D on the musculoskeletal system, where high doses, appear to be harmful with regard to falls, fracture risk, and BMD, especially for people without Vit.D deficiency and at low fracture risk (Anagnostis et al. 2020). A 2020 meta-analysis, using age over 60 as a criterion and based on a total of 41,738 participants and 5916 patients (including 3,237 hip fractures), indicated that serum 25 hydroxyvitamin D levels were negatively correlated to the risk of hip fracture (N. Wang et al. 2020). However, the authors concluded that high serum Vit.D protects against the risk of hip fracture and vote in favor of supplementation.

Consistent with these findings, a meta-analysis including up-to-date randomized controlled trials (RCTs) with more than 100,000 patients found that a daily Vitamin D dose of 800 to 1,000 IU was the most probable way to reduce the fracture and fall risk (Kong et al. 2022).

Gender

Gender also plays an important role in fracture risk, as postmenopausal hormonal modifications negatively impact the quality of the bone (Johnell and Kanis 2006). In addition, females presented an increased risk of falling compared to males, which itself is an independent predictor of FFs (Kalyan and Johansson 2009; Roy et al. 2002). Studies to date have shown a significant association with the female gender, a finding that accords with the higher incidence of osteoporosis in females (Breuil et al. 2008; Maier et al. 2016; Chaplin 2021).

Medicine Use

Several drugs increase the risk of FFs. Among the more recent classes of drugs, the use of oral or systemic glucocorticoids is a critical factor that may influence the risk of FFs (van Staa et al. 2000; Reid et al. 2000; 2009; Saag et al. 2019; 2007). Several studies have reported that treatment with corticosteroids at any dose orally for three months or more, or glucocorticoid treatment with ≥5 mg prednisolone daily or equivalent for three months or more, can increase the risk for fracture (J A Kanis et al. 2013; Chaplin 2021; Adami et al. 2011). Such treatments, produce a negative effect on bone causing rapid bone-quality loss, and BMD depletion. Hormone-blockade treatments involving the use of aromatase inhibitors for females operated for breast cancer and GnRH agonists for males with prostate cancer, lead to a reduction of BMD but at a slower rate and have been associated with increased risk for fractures (Chaput and Sumar 2022; Hadji 2009). Other drugs involved in fracture risk, are selective serotonin reuptake inhibitors (SSRI), proton pump inhibitors (PPI), H2 inhibitors, anticonvulsants, loop diuretics, anticoagulants, excess of thyroid hormones, and antiretroviral treatment (J A Kanis et al. 2013).

Concerning the relationship between PPIs, bone disease, and fractures, though multiple observational studies have demonstrated an association

between PPIs and FFs, the lack of a proven mechanism through which PPIs increase the risk of fracture suggests that this association may not be causal (Targownik and Leslie 2011). Currently, it is not recommended to discontinue PPIs in individuals with a history of fracture or increased risk of fracture, however, clinicians should make efforts to avoid using PPIs in situations where benefits are minimal or clinical indications are lacking (Fattahi et al. 2019).

Additional risk factors for osteoporosis and FFs involve higher intake of phosphorus, benzodiazepine use, alcohol intake of three or more units daily, vitamin D deficiency, and reduced calcium intake which is a major risk factor for FFs (Pinheiro et al. 2008; Adami et al. 2011; Loh et al. 2008; Maier et al. 2016; J A Kanis et al. 2013). Using bone-depleting drugs such as thyroid hormone and furosemides, also significantly increases the risk for FFs (Loh et al. 2008).

Family History of Osteoporosis/Fractures, and Premature Menopause

A positive family history of osteoporosis and fractures influences fracture risk independently of BMD (British Orthopaedic Association 2007). Parental hip fracture is significantly associated with a higher risk of hip fractures in offspring and, to a lesser extent, of all other types of osteoporotic fractures (Pinheiro et al. 2008; Adami et al. 2011). Similarly, the presence of a previous fracture, regardless of its' site, particularly of the hip, wrist, and spine, is an important risk factor for further fractures and is also independent of BMD (Adami et al. 2011; JA. 2002; John A Kanis et al. 2005; Wainwright et al. 2005; Siris et al. 2004; Schuit et al. 2004).

The most common prognostic fractures are those of the vertebrae, hip, humerus, and wrist. Moreover, the risk of further fractures increases with the number of previous fractures, as patients with three or more previous fractures have a ten times greater risk of fracture than patients who have never suffered from fractures (Adami et al. 2011). In postmenopausal women, the increased fracture risk is highest after any clinical fracture, and the risk is independent of the location of the fracture, whereas the risk of subsequent fracture is doubled (van Geel et al. 2008; Klotzbuecher et al. 2000). Moreover, menopause before the age of 47 has been associated with an increased risk of sustaining FFs and an increased incidence of osteoporosis at 77 years of age (O Svejme et al. 2012).