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Reprint of: The impact of fragility fracture and approaches to osteoporosis risk assessment worldwide☆

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A B S T R A C T

Osteoporosis constitutes a major public health problem, through its association with age-related fractures, particularly of the hip, vertebrae, distal forearm and humerus. Substantial geographic variation has been noted in the incidence of osteoporotic fractures worldwide, with Western populations (North America, Europe and Oceania), reporting increases in hip fracture throughout the second half of the 20th century, with a stabilisation or decline in the last two decades. In developing populations however, particularly in Asia, the rates of osteoporotic fracture appears to be increasing. The massive global burden consequent to osteoporosis means that fracture risk assessment should be a high priority amongst health measures considered by policy makers.

The WHO operational definition of osteoporosis, based on a measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA), has been used globally since the mid-1990s. However, although this definition identifies those at greatest individual risk of fracture, in the population overall a greater total number of fractures occur in individuals with BMD values above threshold for osteoporosis diagnosis. A number of web-based tools to enable the inclusion of clinical risk factors, with or without BMD, in fracture prediction algorithms have been developed to improve the identification of individuals at high fracture risk, the most commonly used globally being FRAX®. Access to DXA, osteoporosis risk assessment, case finding and treatment varies worldwide, but despite such advances studies indicate that a minority of men and women at high fracture risk receive treatment. Importantly, research is ongoing to demonstrate the clinical efficacy and cost-effectiveness of osteoporosis case finding and risk assessment strategies worldwide. The huge burden caused by osteoporosis related fractures to individuals, healthcare systems and societies should provide a clear impetus for the progression of such approaches.

Introduction

Over the last 3 decades, osteoporosis has been transformed from being viewed as an inevitable consequence of ageing to the disease which is readily assessed, and for which we now have a wide range of effective pharmacological therapies. The definitional approach to osteoporosis has changed markedly over this time. Thus the original histological definition was based on low bone mass and microarchitectural deterioration of bone tissue, resulting in bone fragility (Consensus development conference, 1993). Clearly this is somewhat cumbersome in clinical practice, requiring, in the absence of high resolution peripheral quantitative computed tomography (HR-pQCT), a bone biopsy to make the diagnosis, and in the mid-1990s the World Health Organisation (WHO) convened a working group to generate an operational definition of osteoporosis, which could be used to provide a standardised case definition in epidemiological studies. Here osteoporosis is defined as a BMD (with the reference site now being the femoral neck) that is 2.5 standard deviations or more below the young adult female mean

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(World Health Organization Study, 1994). This operational definition has evolved into the clinical diagnostic definition of osteoporosis, and serves well where a diagnostic label is required. However it is readily apparent that although low BMD identifies individuals at increased risk of fracture, the majority of fragility fractures occur in individuals who have less marked reductions in bone mass or normal BMD, since although individually at lower risk, there are numerically far more in this population (Kanis et al., 2007). This consideration has led to more detailed assessments of bone itself, for example delineation of microarchitectural parameters using HR-pQCT, and more pragmatic approaches combining BMD with clinical risk factors partly independent of BMD in absolute risk calculators such as the web-based FRAX® algorithm (Kanis et al., 2007). In this review we will describe the variation in the burden of fragility fracture and high fracture risk globally, setting the worldwide context for the absolute necessity of both primary and secondary approaches to fracture risk assessment and subsequent treatment, before describing these approaches and highlighting some of the pressing issues currently facing clinicians and policy-makers aiming to reduce the global impact of fragility fracture.

Epidemiology and geography of high fracture probability

The Global Burden of Disease study demonstrated a massive impact of musculoskeletal conditions on populations worldwide: the number of disability adjusted life years (DALYs) attributable to musculoskeletal disorders has increased by 17.7% between 2005 and 2013 (Murray et al., 2015). “Low back pain” ranked top, “neck pain” fourth, “other musculoskeletal” tenth, and “osteoarthritis” thirteenth in the WHO rankings of causes for years lived with disability worldwide in 2013 (Global et al., 2015), with osteoporotic fractures playing a major part in the “back pain” and “other musculoskeletal” categories. The 2004 US Surgeon General's report estimated that 10 million Americans over the age of 50 have osteoporosis, leading to 1.5 million fragility fractures each year (Bone Health and Osteoporosis, 2004), with another 34 million Americans at risk of the disease. Economically, the cost to the US is around $17.9 billion per annum. In the EU, a report estimated that in 2010, 6.6% of men and 22.1% of women aged over 50 years had osteoporosis, and that there were 3.5 million fragility fractures (Hernlund et al., 2013). The annual direct costs attributable to fracture treatment in the EU equate to approximately €24 billion, though when indirect costs such as long term care and facture prevention therapies are taken into account, this figure rises to €37 billion per year (Hernlund et al., 2013) (Table 1). A British study indicated similar population risks (van Staa et al., 2001), with 1 in 2 women and 1 in 5 men aged 50 years expected to have an osteoporosis-related fracture in their remaining lifetime.

Global variation in fracture rates

Global variation in fracture incidence is best documented for hip fracture, and studies have shown marked heterogeneity in annual age-standardised hip fracture rates. The largest systematic review, published in 2012, used a literature survey covering a 50 year period and UN data on population demography (Kanis et al., 2012). The highest annual age-standardised hip fracture incidences (per 100,000 person-years) were observed in Scandinavia (Denmark (574), Norway (563) and Sweden (539), plus Austria (501). The lowest were found in Nigeria (2), South Africa (20), Tunisia (58) and Ecuador (73). In general, there was a swathe of high risk countries in North Western Europe, Central Europe, the Russian Federation and Middle-Eastern countries such as Iran, Kuwait and Oman. Other high risk countries were Hong Kong, Singapore and Taiwan. Generally low risk regions included Latin America, (with the exception of Argentina), Africa, and Saudi Arabia, as shown in Fig. 1. Discounting the rates for Nigeria and South Africa, which were from either old or unreliable sources, there was around a 10-fold range in hip fracture incidence worldwide, with the overall age-standardised incidence in men being half that of women. In general, the highest incidence of hip fracture is generally observed in countries furthest from the equator and in countries in which extensive coverage of the skin due to religious or cultural practices is the norm, suggesting that vitamin D status may be an important factor underlying this distribution.

The 10 year probability of major osteoporotic fracture (hip, clinical vertebral, forearm or humeral fracture) was calculated for those countries where a FRAX model was available. These fracture probabilities are shown in Fig. 2; in both men and women the lowest probabilities were found in Tunisia, Ecuador, Philippines and China, with the highest rates in Denmark, Sweden, Norway and Switzerland, with the USA (Caucasian population data only), fifth highest. Fracture probabilities, were, on average 23% higher in women than men, which contrasts with overall hip fracture incidence which was twofold higher in women than in men. This closer approximation between the sexes for the probability estimate (which included a BMD measurement) arises because the risk of hip and other osteoporotic fracture are roughly identical in men and women of the same age and femoral neck BMD (Srinivasan et al., 2012; Kanis et al., 2011a; Johnell et al., 2005). The slightly higher probability estimate seen in women reflects the lower death risk in women compared with men.

The reasons for such large worldwide variation in age- and sex-adjusted hip fracture incidence worldwide are not clear. The authors of the systematic review on hip fracture incidence mention the possibilities of inaccurate coding and recording of fractures, the presumption that regional estimates (used in some countries) are representative of overall fracture risk, the fact that over 20% of the included studies were conducted more than a decade previously. Additionally, in some areas of the world, not all hip fracture cases come to medical attention (e.g. in Georgia, 75% of patients with hip fracture are not hospitalised, and in Kazakhstan and Kyrgyzstan 50% are not hospitalised (The Eastern European, 2011) due to poor access to surgical services and affordable medical care). However, such problems would not undermine the principal finding of 10 fold differences in hip fracture risk, and in 10 year fracture probability worldwide. Genetic differences may go some way towards explaining the differences in fracture risk (for example, Black people in the USA have lower fracture probabilities than Caucasians), but the fact that immigrant populations show acclimatisation to local fracture rates (for example, the incidence of hip fracture in Black people in the USA is much higher than in Africans) (Cauley et al., 2011), suggests that environmental factors are more important. Previously identified risk factors for osteoporosis (which will be discussed in more detail later in this review), such as low body mass index, low bone mineral density, poor calcium intake, reduced sunlight exposure, early menopause, smoking, alcohol use,

Table 1
Impact of osteoporosis-related fractures across Europe. Data derived from (Hernlund et al., Archives of Osteoporosis, 2013).

	Hip	Spine	Wrist
Lifetime risk in Women (%)	23	29	21
Lifetime risk in Men (%)	11	14	5
Cases/year	620,000	810,000	574,000
Hospitalization (%)	100	2–10	5
Relative survival	0.83	0.82	1.00

Costs: All sites combined ~ €37 billion.