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RESEARCH ARTICLE

Clinical, biochemical, and densitometric profiles and FRAX risk calculations of South African patients with fragility fractures of the hip: observations from a tertiary care centre

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Purpose: Although fragility hip fractures (HF) in the South African (SA) population are among the lowest worldwide, the incidence of HF is expected to more than double over the next few decades. Little is known about the contributors to increased hip fracture risk, including low bone mineral density (BMD), in our unique population. In addition, the ability of the recently calibrated SA Fracture Risk Assessment Tool (FRAX) to identify high fracture risk in the SA population accurately has not been validated.
Methods: A retrospective, descriptive, cohort study of SA postmenopausal women and men ≥ 50 years who presented with fragility HFs was conducted. The ability of clinical risk factors (CRFs) and BMD measured by dual-energy X-ray absorptiometry (DXA), as well as calculated FRAX probability scores, to identify the known high fracture risk in SA patients were evaluated. The SA FRAX tool was used, and a high fracture risk defined if the United States (US) fixed thresholds for major osteoporotic (MOF) and/or HF risk were exceeded (≥ 20% and ≥ 3% over 10 years respectively).
Results: A total of 163 patients were included. The most useful predictive CRFs were age and gender, recreational toxins in men, and a history of falls. Most were females (71%), who were older than males. DXA-BMD and FRAX-HF calculations best identified the known high fracture risk in the study cohort. FRAX-MOF calculations performed poorly.
Conclusion: Fracture risk assessment tools did not identify the known high fracture risk in all of the elderly study cohort with HF. Clinicians must continue to appreciate the important role of a good clinical assessment to ensure optimal fracture risk prediction.

Keywords: DXA-BMD, elderly, FRAX calculations, hip fracture, South Africa

Introduction

Osteoporosis (OP) is common in the elderly and the association with fragility fractures is well established.[1] The disease is silent and remains widely unrecognised until the patient presents with a fracture.[2] Management is often limited to the surgical aspects and not focused on secondary fracture prevention and treatment of the underlying condition.[3] Epidemiological data confirm a marked increase in hip fracture incidence globally, and it is estimated that by 2050 there will be more than 6 million hip fractures worldwide.[4]

This rise is mainly attributed to increased ageing globally,[5] especially in developing countries.[6] Hip fractures (HFs) are the most serious osteoporotic fracture and their detrimental consequences are well known.[5,6] A HF can be life changing and carries with it a significant impact on mortality, quality of life, mobility, independence, and an increased risk of future osteoporotic fractures.[5] Data pertaining to HF incidence amongst South Africans are limited. A very low hip fracture rate in Black Africans was documented by Solomon and Africa[7] many decades ago. Significantly (tenfold) higher hip fracture rates amongst a Black African subpopulation in the eThekwini region of KwaZulu-Natal were reported in a more recent study. Most recently, a multicentre multi-ethnic study involving three of the nine provinces of SA supported this marked increased in hip fracture incidence amongst Black Africans (age-adjusted hip fracture rate of 69.2 per 100,000 p.a. for women and 73.1 per 100,000 p.a. for men). These rates, however, remain amongst the lowest globally.[8,9] Of note was the marked ethnic variation in hip fracture risk amongst South Africans in this study with significantly higher HF rates noted among White and Indian populations.[9]

Bone mineral density (BMD) measured by central dual-energy X-ray absorptiometry (DXA) is a very good surrogate marker of bone strength and a cornerstone of OP management.[10,11] The inverse relationship between BMD and incident fracture, combined with clinical risk factors (CRFs), is used to guide clinical management.[12–14] World Health Organization (WHO) criteria for OP based on BMD do not identify everyone at risk of fracture, especially in the elderly population. Data derived from the Study of Osteoporotic Fractures showed that almost half of all fragility fractures at multiple sites occur in individuals with a femoral neck (FN) T-score of > −2.5.[15]

The WHO Fracture Risk Assessment (FRAX) tool has been developed to provide a more integrated assessment of fracture risk, especially in the elderly.[16–18] It determines a 10-year absolute risk of fracture in an individual based on genotype (family history), phenotype, the presence of robust CRFs for OP that

impact on bone strength due to their effect on bone quantity and bone quality, and a FN-BMD if available.[17] The FRAX tool is used and tested in many countries across the world and was also recently calibrated for the SA population.[19]

Little is known regarding the demographic, clinical, and biochemical profile of SA adult men and postmenopausal women with fragility hip fractures, i.e. fractures that occur secondary to trauma equivalent to falling from a standing height. The contribution of low BMD to hip fracture risk remains uncertain. The ability of recommended calculated FRAX based intervention thresholds from the United States (US) to identify SA patients at increased risk of fracture has not yet been evaluated in our unique and diverse population. This study describes the clinical, biochemical, and densitometric profile of patients with fragility HFs presenting to a resource-limited tertiary centre in SA. The sensitivity of a BMD and of calculated FRAX probability scores to predict the known high fracture risk in this cohort was assessed.

Materials and methods

Study population

This retrospective, descriptive, cohort study was conducted at a tertiary academic hospital situated in the Cape province, SA. All postmenopausal women and men aged 50 years and older who present to this health facility with fragility proximal hip fractures are routinely referred from Orthopaedics to the Endocrine Division for a detailed bone mass and future fracture risk assessment. Hip fracture cases who attended this visit from May 2018 to April 2022 were eligible for study entry and enrolled consecutively. The research was conducted according to the ethical guidelines and principles of the International Declaration of Helsinki and the SA Guidelines for Good Clinical Practice and the study was approved by the Stellenbosch University Health Research and Ethics committee (HREC ref S21/11/256).

Demographics and CRFs for osteoporosis

A routine demographic and CRF questionnaire included documentation of age, gender, self-reported ethnicity, family history of osteoporosis or first-degree relative with hip fracture, personal health, lifestyle, reproduction, recent falls, and fractures. Lifestyle questions included the use of alcohol (total units daily and weekly), smoking (current and pack years) and activity level prior to injury. A history of prior fragility fractures and fall propensity was obtained. Information pertaining to CRFs obtained with the demographic and clinical risk questionnaire was further supported by clinical patient data retrieved from the Tygerberg Electronic Content Management System (ECM) and with biochemical evaluations where relevant.

Anthropometry

Basic anthropometric measurements (weight in kilograms and height in centimetres) were taken by a single investigator using the same calibrated devices. Body mass index as kilograms/centimeter^2 (BMI) values was divided into weight categories according to the WHO classification.[20]

Densitometry

The DXA Hologic Discovery W QDR system (serial number 87664) was employed to measure BMD and was analysed using software version 13.4.2 (Scientific Division of Hologic Inc, Marlborough, MA, USA) by a single and experienced DXA technician. The DXA scan was used to determine areal BMD of the non-fractured hip and the spine and to perform a lateral vertebral assessment (LVA). The femoral neck (FN), total hip (TH), and lumbar spine (LS) BMD were measured. A BMD T-score of ≤ -2.5 at any one or more of the above-mentioned sites was regarded as a BMD in keeping with a diagnosis of osteoporosis, whereas a BMD T-score of < -1 to > -2.5 was considered to indicate low bone mass referred to as osteopenia, in accordance with the WHO diagnostic criteria.[10] The T-score was calculated by comparing the measured BMD of the patient, irrespective of gender or ethnicity, with the expected peak BMD of a uniform white female reference population (NHANES female dataset).[10] An LVA formed part of the DXA assessment, providing information on vertebral structure and to detect prevalent morphometric vertebral fractures (VFs) (defined according to the visual, semi-quantitative Genant's assessment).[21]

Biochemistry

Laboratory analyses were performed on-site by the Tygerberg Hospital National Health Laboratory Service (NHLS). Investigations performed included a full blood count, serum creatinine, total calcium, albumin, phosphate, magnesium, and 25-hydroxyvitamin D (25[OH]D) levels. Commercial assays were used according to the manufacturer's protocol. A Cobas® analyser (Roche, Basel, Switzerland) was used for the measurement of both serum total calcium (spectrophotometric detection) and 25(OH)D (electrochemiluminescence binding assay). The normal reference range for total calcium is 2.20–2.55 mmol/l. Twenty-five hydroxy vitamin D levels are expressed in nmol/l and the NHLS in accordance with the 2011 Endocrine Society guideline defined 25(OH)D as either deficient (< 30 nmol/l), insufficient (30.1–50 nmol/l), or sufficient (> 50 nmol/l).[22]

FRAX calculation

A FRAX score was calculated with and without inclusion of the FN-BMD employing the SA ethnic and gender-specific FRAX model.[19] The current HF was not included in the calculation. The purpose of the FRAX calculation was not, in the specific study cohort, to determine the need for intervention as the presence of a fragility proximal HF already fulfilled diagnostic criteria and qualified the patient for active intervention. The ability of the locally calibrated FRAX tool to identify our study participants as being at high risk of their sustained hip fracture or subsequent fracture requiring immediate bone protection was assessed. This was based on exceeding globally accepted fixed US intervention thresholds (IT) (10-year HF probability of $\geq 3\%$ and/or 10-year probability of a major OP fracture (MOF) $\geq 20\%$).[17]

Data analysis and statistical analysis

Patient information and data were entered onto a spreadsheet using Excel version 2016 (IBM Corp, Microsoft, Redmond, WA, USA) and statistical analyses performed using Statistica (v13.5, TIBCO Software, https://www.statsoft.de/en/data-science-applications/tibco-statistica/). Continuous data are described using means and standard deviations, or medians and interquartile ranges, as appropriate based on distribution. Categorical variables are described using frequencies and percentages. Differences between groups were investigated with independent t-tests or Mann–Whitney U tests for continuous data, or chi-square tests for categorical data. An alpha-level of < 0.05 was considered significant.

Table 1: Characteristics and CRFs for osteoporosis in the total cohort and in the female and male cohorts respectively

Description	Total cohort ($n = 163$)	Female cohort ($n = 115$)	Male cohort ($n = 48$)
Age *n/N*	163/163	115/115	48/48
Average (years)	73.6 ± 10.2	74.8 ± 10.6	70.8 ± 8.7
< 70 years, *n* (%)	58 (37%)	38 (33%)	22 (46%)
70–79 years, *n* (%)	48 (28%)	28 (24%)	18 (38%)
≥ 80 years, *n* (%)	57 (35%)	49 (43%)	8 (17%)
Ethnicity, *n/N*	163/163	115/115	48/48
White, *n* (%)	64 (39%)	49 (43%)	15 (31%)
Black, *n* (%)	9 (6%)	6 (8%)	3 (6%)
Mixed ancestry, *n* (%)	90 (55%)	60 (52%)	30 (63%)
Parent with hip fracture, *n/N*	153/163	109/115	44/48
Yes, *n* (%)	9 (6%)	5 (5%)	4 (9%)
Activity level in last year *n/N*	153/163	109/115	44/48
Inactive, *n* (%)	41 (27%)	29 (27%)	12 (27%)
Active (ambulant indoors only), *n* (%)	29 (19%)	23 (21%)	6 (14%)
Active (ambulant in & outdoors), *n* (%)	83 (54%)	57 (52%)	26 (59%)
Falls in year prior to hip injury, *n/N*	148/163	105/115	43/48
Yes, *n* (%)	44 (30%)	36 (34%)	8 (19%)
Once, *n* (%)	11 (7%)	9 (9%)	2 (5%)
Multiple, *n* (%)	33 (22%)	27 (26%)	6 (14%)
Fragility fracture prior to hip injury, *n/N*[a]	149/163	106/115	43/48
Peripheral clinical fracture, *n* (%)	36 (24%)	27 (25%)	9 (21%)
Smoking, *n/N*	153/161	109/115	44/48
Current smoker, *n* (%)	38 (25%)	19 (17%)	23 (52%)
Never smoker, *n* (%)	76 (50%)	70 (4%)	6 (14%)
Pack years in smokers	20.3 (10.0–29.0)	22.4 (7.5–29.0)	20.0 (14.0–39.0)
Alcohol intake, (*n/N* = yes/ cohort)[b]	49/153	26/110	23/43
> 2 units daily in intake cohort, *n* (%)	6 (12%)	0	6 (26%)

Available datasets for participant characteristics and CRFs indicated by *N*. Ethnicity as self-reported by patient; [a]known fragility fractures prior to hip injury, [b]alcohol intake noted only for patients who reported use of alcohol.

Results

Characteristics of the study participants and CRFs for OP

A total of 163 patients, 71% female ($n = 115$) and 29% male ($n = 48$), were assessed following presentation at Tygerberg Hospital with a fragility fracture of the proximal hip and thus were eligible for study entry. The characteristics and CRFs for osteoporosis and fracture are summarised in Table 1. The mean age was 74 ± 10 years with the mean age of males younger than that of females ($p = 0.021$). Some 83% of males (n/N = 40/48) were younger than 80 years of age, whilst only 57% (*n/N* = 66/115) of females were younger than 80. The study cohort was represented by 55% of patients of mixed ancestry (*n/N* = 90/163) and 39% (*n/N* = 64/163) White with few Black and no Indian patients.

The majority of patients (73%) were active and independent prior to the hip injury with 54% of the cohort indicating participation in both indoor and outdoor activities. In total, 30% of study patients reported a fall in the last year. Women were more likely to fall and most men and women who reported prior falls fell more than once. Previous fragility fractures were documented in 36 patients. Most fractures reported were either prior wrist ($n = 11$) or prior contralateral hip fractures ($n = 12$). Four patients sustained successive hip fractures during the study period, thus totalling 16 individuals with fractures of both hips (*n/N* = 16/163; 10% of the cohort). Information on the mode of the current hip injury was available in 157 participants with the injury following a fall from standing height in 143 (91%). A high percentage of males were active smokers (52%) but only six males admitted to excess alcohol intake defined as three or more units (one unit = 8–10 gram of alcohol) daily (6/23; 26%). The most prevalent comorbid condition was hypertension (*n/N* = 97/163; 59%) followed by diabetes mellitus (12%) and cerebrovascular disease (11%). HIV status was positive in only 3 females based on in-house biochemical confirmation obtained in 74 of the study patients.

Anthropometry, fracture information, and biochemistry

Anthropometry, hip fracture information, and Vitamin D status are detailed in Table 2. The mean BMI was within the normal weight WHO BMI classification for the total study cohort and in the female and male cohorts (23.3 ± 5.3; 24.0 ± 5.4, and 21.8 ± 4.6 kg/m^2 respectively). Most of the overweight and obese hip fracture cases were female (*n/N* = 42/52; 78%), of whom 15 females and 1 male had BMIs within the WHO obese classification (BMI ≥ 30 kg/m^2). Fracture of the femoral neck was the most prevalent fracture in both females and males. Encountered biochemical abnormalities were confined to hypocalcaemia and insufficient or deficient 25(OH)D levels. Hypocalcaemia was mild in most: ≥ 2.10 mmol/l (*n/N* = 33/53; 62%); 2.00–2.09 mmol/l (*n/N* = 20/53; 38%) (normal range

Table 2: Anthropometry, fracture type, and Vitamin D status in the total cohort and in the female and male cohorts respectively

Description	Total cohort (*n* = 163)	Female cohort (*n* = 115)	Male cohort (*n* = 48)
Anthropometry, *n/N*	163/163	115/115	48/48
Weight (kg)	59.5 ± 14.3	58.8 ± 14.2	61.1 ± 14.6
Height* (cm)	159.7 ± 8.3	156.6 ± 7.0	167.1 ± 6.3
BMI* (kg/m^2)	23.3 ± 5.3	24.0 ± 5.4	21.8 ± 4.6
Hip fracture type			
Intracapsular (NOF), *n/N* (%)	98/163 (60%)	70/115 (61%)	28/48 (58%)
Extracapsular (IT/ST), *n/N* (%)	43/163 (26%)	29/115 (25%)	14/48 (29%)
Unspecified	22/163 (13%)	16/115 (14%)	6/48 (13%)
25(OH)D assessment			
Average (mmol/l)	39.0 (28.0–50.0)	39.0 (29.0–50.0)	37.5 (26.0–50.0)
Normal, *n/N* (%)	33/141 (23%)	24/97 (25%)	9/44 (21%)
Insufficient, *n/N* (%)	65/141 (46%)	43/97 (44%)	22/44 (50%)
Deficient, *n/N* (%)	43/141 (30%)	30/97 (31%)	13/44 (30%)

BMI – body mass index; NOF – neck of femur fracture; IT – intertrochanteric fracture; ST – subtrochanteric fracture; unspecified refers to cases where knowledge re fracture type not available. 25(OH)D 25-hydroxy-vitamin D. 25(OH)D regarded as normal if > 50 mmol/l; insufficient 30.1–50 nmol/l or deficient if ≤ 30 nmol/l.

2.20–2.55 mmol/l) (detail regarding additional biochemical data added as Supplementary data A). Vitamin D insufficiency and deficiency were present in 46% and 30% of the study patients respectively.

BMD and structural vertebral assessment

A DXA scan was performed in 162 of the 163 study participants (detail regarding densitometry results and the structural vertebral assessment added as Supplementary data B). The presence of bilateral hip fractures in 16 patients and inability to position optimally on the DXA machine precluded an additional 7 patients from the evaluation of proximal hip BMD and 1 patient from an accurate assessment of lumbar BMD. Densitometric findings are illustrated in Figure 1. Most patients (*n/N* = 117/162; 72%) had BMD values in keeping with OP, defined as a BMD ≤ −2.5 at any of the major measured sites (lumbar, TH, or FN region). More females had OP compared with males (77% versus 60%). BMD was normal in only two (2%) females and four (8%) males (Figure 1A). In the cohort where accurate hip assessments were possible, OP was present in 73% (*n/N* = 102/139). In those with confirmed OP, an FN-BMD ≤ −2.5 was present in 93% (95/102) and a lumbar BMD ≤ −2.5 was present in 49% (*n/N* = 50/102) (see Figure 1B).

Unknown morphometric VFs were identified on the DXA-LVA in 51% of the study cohort; fractures were mostly multiple and involving both thoracic and lumbar vertebrae. A higher percentage of the White cohort (*n/N* = 38/62; 61%) had vertebral fractures compared with the Coloured (*n/N* = 42/88; 48%) and Black groups (*n/N* = 3/9; 33%). Age ($p = 0.146$) and anthropometry (weight: $p = 0.567$; height: $p = 0.207$; BMI: $p = 0.985$) were similar in those with or without vertebral fractures. Proximal femoral BMD measurements were lower, and MOF and HF risk based on FRAX calculations were higher in the cohort with VF compared with those with normal vertebral structure ($p < 0.05$; $p = 0.014$ respectively).

FRAX calculated 10-year probability of major osteoporotic or hip fracture risk

The FRAX calculation that best identified the known high fracture risk in the study patients was the HF 10 years probability percentage at a fixed threshold of ≥ 3% (see Table 3). The calculated HF prediction performed better in females. The percentage of females identified to be at high fracture risk based on a FRAX-HF calculation without inclusion of BMD data, with inclusion of BMD data, or with inclusion of BMD data and VFs

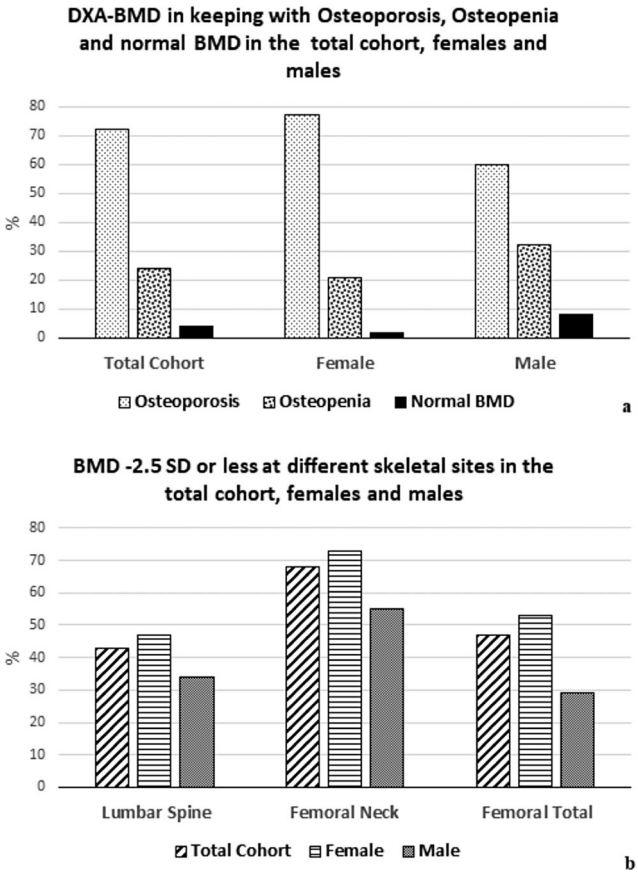

Figure 1: (A) Percentage of study patients with DXA-BMD in keeping with OP, osteopenia, or with a normal BMD. Classification based on the lowest reading for either the lumbar spine, femoral neck, or total femoral region. (B) Percentage of study patients within the total cohort and in females and males with a BMD measurement of ≤ −2.5SD for the lumbar spine, femoral neck, or total femoral region respectively.

Table 3: FRAX calculated 10-year probability of MOF and hip fracture in the total cohort and in the female and male cohorts respectively

Description	Total cohort (*n* = 163)	Female cohort (*n* = 115)	Male cohort (*n* = 48)
FRAX fracture probability (DXA BMD not included)			
MOF (%), *n/N*	152/163	109/115	43/48
Average score**	6.9 (3.7–11.0)	8.8 (5.1–13.0)	3.7 (2.5–4.7)
≥ 20%, *n* (%)	13 (9%)	13 (12%)	0
Hip fracture (%), *n/N*	152/163	109/115	43/48
Average score**	2.6 (1.3–6.0)	4.0 (1.6–7.0)	1.7 (1.2–2.4)
More or equal to 3%, *n* (%)	74 (49%)	66 (61%)	8 (19%)
FRAX fracture probability (DXA BMD included)			
MOF (%), *n/N*	133/163	98/115	35/48
Average score**	7.8 (4.5–12.0)	9.4 (6.1–15.0)	4.2 (3.2–6.7)
≥ 20%, *n* (%)	9 (7%)	9 (9%)	0
Hip fracture (%), *n/N*	133/163	98/115	35/48
Average score**	3.5 (1.8–6.5)	4.0 (2.1–7.0)	2.3 (1.3–3.5)
≥ 3%, *n* (%)	78 (59%)	65 (66%)	13 (37%)
FRAX fracture probability (DXA BMD and LVA vertebral fractures included)			
MOF (%), *n/N*	133/163	98/115	35/48
Average score**	9.0 (5.3–16.0)	11.0 (7.8–17.0)	5.6 (3.6–7.6)
≥ 20%, *n* (%)	15 (11%)	15 (15%)	0
Hip fracture (%), *n/N*	133/163	98/115	35/48
Average score**	3.9 (2.2–7.2)	5.0 (2.7–8.6)	2.9 (1.7–4.2)
≥ 3%, *n* (%)	85 (64%)	69 (70%)	16 (46%)

if present were 61%, 66%, and 70% respectively. The FRAX-MOF calculation at a fixed threshold of ≥ 20% identified less than 15% of study patients to be at high risk of fracture. The FRAX-MOF calculation performed better in females; no male subject reached the US criteria for high fracture risk based on the FRAX-MOF calculation per se.

Data are expressed as *n*%, mean* ± SD or median** (interquartile range); high fracture risk based on exceeding the US fixed FRAX calculated thresholds of ≥ 20% and ≥ 3% for MOF and hip fracture respectively as indicated in bold. Current hip fracture and unknown vertebral fracture(s) were not included in calculation of FRAX score *without* BMD. Undiagnosed vertebral fracture of unknown duration were included as a prior fragility fracture in the FRAX calculation in those who underwent BMD with LVA.

WHO-BMI weight categories and BMD

Most of our HF cohort were of normal weight. In women, 15% were underweight and 38% categorised as either overweight or obese based on WHO-BMI criteria. About a fifth of men were either underweight or overweight with only one male categorised as obese. In our HF patients, BMD expressed as T-scores in both spine and hip regions were lowest in the underweight group and higher in the overweight/obese categories compared with normal-weight patients (see Figure 2). This was true for all measured sites and in both genders. Most hip fractures in our study occurred amongst the underweight and normal-weight patients (108/163); (66%).

Discussion

To curb the escalating prevalence of hip fractures globally and locally, early identification of at-risk patients with active

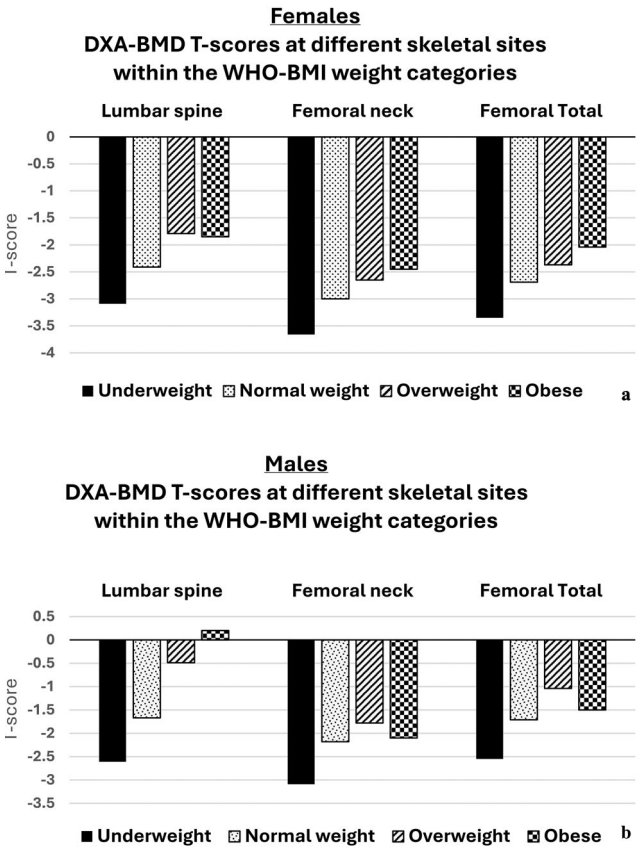

Figure 2: (A) DXA-BMD T-scores for the lumbar spine, femoral neck, and total femoral region within the WHO-BMI weight categories in females. (B) DXA-BMD T-scores for the lumbar spine, femoral neck, and total femoral region within the WHO-BMI weight categories in males.

screening programmes is of paramount importance. This entails the recognition of CRFs, assessing fall risk and utilising available diagnostic tools such as DXA-BMD and FRAX calculations. In this study of elderly patients with fragility hip fractures, most were women (115/163, 71%). The most useful predictive CRFs for skeletal fragility and fracture were age and gender, smoking, and excessive alcohol intake (mostly in men) and a history of falls. FN-BMD alone and FRAX-HF calculations inclusive of FN-BMD best identified the known high fracture risk in our study cohort. The FRAX-MOF (with or without BMD) calculation proved to be a poor indicator of high hip fracture risk in elderly SA patients when employing the ≥ 20% 10-year risk thresholds. Vitamin D insufficiency or deficiency was present in 76% of the cohort.

Hip fracture risk in the SA population is lower compared with many other countries worldwide and varies widely amongst our diverse ethnicities. The risk is highest in the White population, followed by the Indian, mixed and African ethnic groups.[9] This study group contained mostly White and mixed-ancestry patients with few Black and no Indian patients. This is typical of the Western Cape but not for the greater SA. The incidence of hip fractures in SA has increased in the last few decades and based on estimated projections is expected to more than double over the next three.[23] These projections are similar to those of other countries in sub-Saharan Africa and are ascribed to increased urbanisation and improved longevity.

Clinical risk factors (CRFs)

Increasing age and female gender represent important CRFs for fragility HFs, in this and other studies. The decline in bone strength in the elderly is due to age-related decline in bone quantity and quality, coupled with the cumulative effects of adverse lifestyle and environmental exposures.[5,6] The fracture risk is further enhanced due to age-related sarcopenia and increased fall risk. The accelerated physiological bone loss at menopause, in addition to the effects of ageing and the environment, makes older females more likely to suffer a hip fracture than males.[4,6]

In a recent multicentre, prospective study that reported HF incidence among the four major ethnic groups in SA, the incidence of HFs was higher in women compared with men in all the older age categories.[9] The study also documented a marked increased hip fracture incidence rate with increasing age in both genders and across all ethnic groups, comparable to global epidemiological data.[9]

Males presented at a younger mean age (70.8 ± 8.7 years), compared with females (74.8 ± 10.6 years [$p = 0.021$]). Significantly more females compared with males were ≥ 80 years (43% versus 17%). In the multicentre SA HF incidence study, the median age of study participants was 75 years with men also significantly younger than women (69 versus 77) in the total cohort ($p < 0.001$) and in all four ethnic groups ($p < 0.001$). The literature, in contrast, mostly reports an increase in the prevalence of HFs at an earlier age in females compared with males, the explanation being the higher peak bone mass obtained and an absent male equivalent to menopause. What is noteworthy in our study, and in the multicentre SA HF study, was the significantly higher number of females ≥ 80 years. The younger age of men with fracture in these studies may thus in part reflect reduced longevity and not merely an earlier onset of fractures. Activity levels prior to the hip injury were similar in both genders, but a higher percentage of males reported use of recreational toxins. More adverse environmental exposures in males may have contributed, along with reduced longevity, to the younger mean age of our males with HFs.

Traditionally, lower BMI is considered a risk factor for fracture, whereas obesity was regarded to be favourable towards bone metabolism, this belief being supported by the positive correlation between BMD and BMI and the lower incidence of hip fractures in obese adults.[24,25] In our HF patients, BMD expressed as T-scores in both spine and hip regions was lowest in the underweight group and higher in the overweight/obese categories compared with normal-weight patients. This was true for all measured sites and in both genders. An earlier study exploring potential contributors to bone health in otherwise healthy SA Black and White women also documented a consistent and positive correlation between weight and BMD in pre- and postmenopausal women.[26] Over the last few years, epidemiological and clinical studies have challenged this belief, with studies concluding that obesity in fact increases fracture risk.[27] The risk for some non-vertebral fractures, such as proximal humerus, upper leg, and ankle, is higher in obese adults compared with those of normal weight, whereas the risk is lower in the spine and proximal femur.[28,29] The association between obesity and fracture risk thus remains controversial with a varied and site-specific impact of obesity on fracture risk. Although most hip fractures in our study occurred amongst the underweight and normal weight patients, fractures still happened in overweight or obese individuals, which contests a universal protective effect of excess bodyweight against HF.

DXA

The relationship between BMD and fracture risk is firmly established in White postmenopausal women.[12] The contribution of low BMD to HF risk in elderly SA men and other ethnic groups remains less certain. BMD is a very good surrogate marker of bone strength,[11] but the limitations of BMD to identify everyone at risk of fracture, especially in the elderly population, has been well recognised and relates to bone qualitative aspects that adversely impact on bone strength as well as frailty, sarcopenia, and fall risk.[30]

BMD, in keeping with OP, was documented in most of our HF cases (117/162; 72%) with females more likely than males to have BMD criteria for OP (77% versus 60%). In the subset of patients in whom proximal hip BMD data were available, BMD correctly identified the high fracture risk in 102/139 (73%), with an FN T-score in keeping with OP noted in 95/139 (68%). Less than half of the patients with FN-BMD criteria for OP had concomitant OP-range BMD in the LS. Only seven patients had BMD criteria for OP based on measurements at sites other than the FN (in the LS in six and based on FT-BMD in a single case). Of those, seven had concomitant FN-osteopenia. The FN-BMD was thus the measurement most predictive of the high fracture risk in our cohort, outperforming both the BMD measurement in the LS and the FT region. A combination of FN-OP and FN-osteopenia correctly identified the high fracture risk in 120/139 (86%) of our HF patients: in 91/101(90%) females and 29/38 (76%) males. Several studies, in accordance with our work, have documented FN-BMD to be a strong predictor of HFs and noted that site-specific measurement of BMD provides the best prediction of fracture risk at that site.[15,31] Data from 12 cohort studies of approximately 39,000 men and women was included in a meta-analysis evaluating the

relationship between BMD and fracture risk by Johnell, Kanis and co-workers.[32] In that study, FN-BMD was found to be a strong predictor of hip fractures both in men and women with a similar predictive ability. At the age of 65 years, risk ratio increased by 2.94 (95% CI = 2.02–4.27) in men and by 2.88 (95% CI = 2.31–3.59) in women for each standard deviation (SD) decrease in BMD. The gradient of HF risk was noted to decrease with age, but the absolute risk still rose markedly with age. In another large meta-analysis of prospective studies, a relative risk of HF of 2.6 (95% CI 2.0–3.5) per SD of decrease in FN-BMD was noted.[12]

VFs are the most common complication of OP.[33] In a multinational study in postmenopausal women newly diagnosed with OP, 68% of the subjects had an undiagnosed VF.[34] Most VFs occur during normal activities and are asymptomatic, with only 40% occurring after a fall. Due to their silent nature, most fractures are undiagnosed and not referred for appropriate treatment. Unknown, mostly multiple, morphometric vertebral fractures were identified by DXA-LVA in more than half of our HF patients, affecting both females and males. Improved surveillance programmes and active screening of high-risk patients for OP may reduce the devastating consequences of hip and vertebral fractures by ensuring early identification of those who need to be actively protected.

FRAX

Identification of high fracture risk and fixed intervention thresholds based on a FRAX calculation has been established in the US based on health economics and utilised by many countries globally.[17] In Europe, some countries have developed a FRAX intervention threshold that is country specific and varies with increasing age.[17] In SA, the ability of recommended FRAX-based intervention thresholds to accurately identify high fracture risk has not been validated. In the interim, supported by a consensus opinion of our local National Osteoporosis Foundation (NOFSA) council, the US fixed intervention thresholds of $\geq$ 3% for a FRAX-HF calculation and $\geq$ 20% for a FRAX-MOF calculation are used as indications for bone-specific therapy in elderly South Africans in the absence of established diagnostic criteria for OP.

An elderly patient with a fragility HF represents an individual at high fracture risk, who has reached an IT and should be actively treated for the underlying bone fragility that is most likely due to osteoporosis. It is thus expected that currently available diagnostic tools in this subset of individuals should indicate high fracture risk and dictate active bone-specific protection.

In our study, the HF-FRAX calculation based on the US fixed threshold of $\geq$ 3% best identified the high fracture risk in our patients and performed better in females. Inclusion of FN-BMD data increased the sensitivity to identify high fracture risk, mostly in males. The FRAX-MOF calculation was an insensitive parameter of fracture risk in both genders, albeit performing slightly better in females. This was true when the FRAX calculation was performed with or without inclusion of DXA data. Not a single male in the cohort was identified as at high fracture risk based on a FRAX-MOF calculation per se.

In the absence of a BMD T-score of –2.5 or less, the FRAX tool identified an additional 6/37 (16%) patients to be at high fracture risk. The FN-BMD measurement in these patients was in keeping with osteopenia in six (6/23; 26%) and was normal in none. Identification of high fracture risk was based on the FRAX-HF calculation in all six, with only one of the six cases noted to also have a FRAX-MOF calculation that was concerning for fracture risk.

The high fracture risk in the cohort with available proximal hip BMD measurements was correctly identified in 95/139 (68%) with the use of an FN-BMD only. This number was increased to 101/139 (73%) with the combined use of an FN-BMD and a FRAX-HF calculation $\geq$ 3% and to 108/139 (78%) with the combination of a BMD at any site and the FRAX-HF calculation $\geq$ 3%.

It must be appreciated that the FRAX calculation, although it provides a more comprehensive assessment of fracture risk compared with BMD per se, has limitations. The timing and type of prior fragility fractures are not quantified, the contribution of smoking is limited to whether the patient is currently smoking or not, and all systemic diseases with potential adverse effects are not included and the disease severity is not considered. Although frailty is to some extent incorporated in the assessment of bodyweight and height, the presence of sarcopenia and resultant fall risk are not included in the FRAX algorithm.

Limitations

Conclusions drawn from this study are limited by the small sample size of 139 that included only 48 male patients. Hospital attendance was impacted on in this low-resource setting due to patient age, reduced mobility, financial constraints, and transport difficulties. Optimal recollection of environmental exposures and identified risk factors proved to be difficult in the elderly. A strength of the study was an experienced DXA technician, who evaluated all the study subjects, thereby ensuring excellent performance and low intra-operator variability.

Conclusion

Available diagnostic and fracture risk assessment tools contribute significantly towards fracture risk prediction, but limitations remain. None of these tools are able to identify everyone at increased risk of fracture. DXA-BMD, especially FN-BMD measurements and FRAX-HF calculations based on US fixed thresholds, best identified the known high fracture risk in our cohort, especially in females. Clinicians must continue to appreciate the important role of a good clinical assessment, which includes evaluation of fall risk, to ensure optimal fracture risk prediction, especially in the elderly.

Ethics

The research was conducted according to the ethical guidelines and principles of the International Declaration of Helsinki and the SA Guidelines for Good Clinical Practice and the study was approved by the Stellenbosch University Health Research and Ethics committee (HREC ref S21/11/256).

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