

Risk Estimates for Hip Fracture From Clinical and Densitometric Variables and Impact of Database Selection in Lebanese Subjects

Mohammad Badra,¹ Abla Mehio-Sibai,² Adina Zeki Al-Hazzouri,³ Hala Abou Naja,² Ghassan Baliki,³ Mariana Salamoun,³ Nadim Afeiche,¹ Omar Baddoura,¹ Suhayl Bulos,¹ Rachid Haidar,¹ Suhayl Lakkis,¹ Ramzi Musharrafieh,¹ Afif Nsouli,¹ Assaad Taha,¹ Ahmad Tayim,¹ and Ghada El-Hajj Fuleihan*³

¹Orthopedics Department, School of Medicine, American University of Beirut, Beirut, Lebanon; ²Epidemiology and Population Health Department, Faculty of Health Sciences, American University of Beirut, Beirut, Lebanon; and ³Department of Internal Medicine, American University of Beirut, Beirut, Lebanon

Abstract

Bone mineral density (BMD) and fracture incidence vary greatly worldwide. The data, if any, on clinical and densitometric characteristics of patients with hip fractures from the Middle East are scarce. The objective of the study was to define risk estimates from clinical and densitometric variables and the impact of database selection on such estimates. Clinical and densitometric information were obtained in 60 hip fracture patients and 90 controls. Hip fracture subjects were 74 yr (9.4) old, were significantly taller, lighter, and more likely to be taking anxiolytics and sleeping pills than controls. National Health and Nutrition Examination Survey (NHANES) database selection resulted in a higher sensitivity and almost equal specificity in identifying patients with a hip fracture compared with the Lebanese database. The odds ratio (OR) and its confidence interval (CI) for hip fracture per standard deviation (SD) decrease in total hip BMD was 2.1 (1.45–3.05) with the NHANES database, and 2.11 (1.36–2.37) when adjusted for age and body mass index (BMI). Risk estimates were higher in male compared with female subjects. In Lebanese subjects, BMD- and BMI-derived hip fracture risk estimates are comparable to western standards. The study validates the universal use of the NHANES database, and the applicability of BMD- and BMI-derived risk fracture estimates in the World Health Organization (WHO) global fracture risk model, to the Lebanese.

Key Words: BMD; Database; Hip fracture; Risk estimates; Risk factors.

Introduction

As a result of the population explosion worldwide, the human, social, and economic costs of osteoporosis will continue to rise (1). Of particular concern is the associated increased incidence of hip fracture, and its high toll in terms

of morbidity, mortality, and economic burden (2,3). Although the incidence and characteristics of osteoporotic hip fracture has been extensively studied in western countries, little is known about the epidemiology of hip fractures in the Middle East. Estimates of hip fracture rates in this region are comparable to those from southern Europe, ranging from 100 to 300/100,000 person-years (4,5); estimates from Lebanon are around 100/100,000 person-years (6,7).

Low bone mineral density (BMD), maternal history of hip fractures, insufficiency fractures, low body weight, tall stature, previous hyperthyroidism, and use of long-acting benzodiazepines or anticonvulsants are significant risk factors of hip fractures (8). Other risk factors include parameters

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*Address correspondence to: Ghada El-Hajj Fuleihan, MD, MPH, Calcium Metabolism and Osteoporosis Program, Department of Internal Medicine, American University of Beirut Medical Center, Bliss Street, Beirut, Lebanon. E-mail: gf01@aub.edu.lb

describing hip geometry (9). BMD is the most powerful single predictor of fractures in general (10), and hip fractures in particular (11–13). For each standard deviation (SD) decrease in the femoral neck density, age-adjusted hip fracture risk increased by 2.6-fold (10).

There are clear differences in BMD in different regions worldwide, with variations of up to 1 SD (14,15), and even greater variations in hip fracture risk (16–19), which are not explained by differences in BMD, suggesting other important differing risk factors for hip fractures between populations. In a population-based cohort, we reported peak BMD in Lebanese subjects to be 0.2–0.9 SD below peak BMD in American subjects, depending on skeletal site and gender (20); other studies from the region demonstrate comparable decrements in peak BMD (21–27). The disparities in BMD between populations have raised uncertainty regarding the preferred BMD database to calculate T-scores and report BMD results, and to derive fracture risk estimates (28). The use of differing BMD databases for the same subject would result in different T-scores, and will affect the diagnosis, and in many instances, the treatment recommended. Currently, both the International Society of Clinical Densitometry [ISCD (29)] and the International Osteoporosis Foundation [IOF (30)] recommend the use of reference range provided by the Third National Health and Nutrition Examination Survey (NHANES III), which is based on femoral neck measurements in white women in the United States aged 20–29 yr (31,32). To our knowledge, no study has validated such recommendation in subjects from non-western origins.

The recently available fracture risk assessment tool (FRAX[®]) is based on the use of clinical risk factors, with or without BMD (<http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=12>). Little is known about the risk factors for hip fracture in the Middle East.

The aim of this study was to evaluate the performance of reported risk estimates from western hip fractures and those derived in a group of Lebanese male and female subjects with hip fractures. This would allow insight into the impact of database selection (population-based Lebanese vs NHANES) on the derived parameters that impact our approach to the patient with osteoporosis:

- 1 T-Score and the diagnosis of osteoporosis using the World Health Organization (WHO) operational definition of the disease (33).
- 2 Fracture risk gradient, expressed as odds ratio (OR) per SD decrease in BMD.

Methods

Participants

The protocol was approved by the Research Committee and the Institutional Review Board of the American University of Beirut, and all subjects signed informed consent.

Of 80 consecutive cases with a hip fracture admitted to our center, 60 were included in the study. Hip fracture patients were eligible to be included in the study if they presented

with the first hip fracture, had both parents of Middle East origin, and were Lebanese residents. Among the 20 patients who were not studied, 4 were not Lebanese, and 16 declined to participate. The control group (N = 90) was chosen from a population-based study of BMD in the elderly (34). Controls were frequency-matched with the hip fracture patients by age and gender with a ratio of 1.5:1. Control subjects were excluded if they had severe osteoarthritis or anatomical hip abnormalities, detected by X-rays; a history of radiotherapy or chemotherapy; a history of nontraumatic fractures; reported intake of steroids, heparin, calcitonin, sex hormones, thyroid hormones, insulin, growth hormones, anticonvulsive medications, bisphosphonates; had previous orthopedic surgery on both hips; reported major chronic diseases (intestines, liver, kidney, heart); reported bed rest for more than 1 mo within 6 mo before the study; had imaging procedure using contrast products within 96 h before presentation; reported avascular necrosis of the hip, rheumatoid arthritis, or congenital hip disease.

Clinical Data Collected

Information on age, height, weight, and body mass index (BMI) was obtained, and these were expressed as continuous variables. Self-reported lifestyle practices and clinical information, including history of previous fractures, presence of major medical problems, use of medications (calcium, vitamin D, multivitamins, sleeping pills, anxiolytics, and drugs to treat osteoporosis), were collected. Information on fall characteristics obtained on study entry included exact time of fall, activity before fall (sitting, standing, walking, changing position, others), reasons for fall (slip, trip, poor lighting, entering bathroom, others), fall direction (sideways, forward, backward, straight down), fall height (fall from horizontal position in bed, from seated position, from standing height), and height fall (1 step, 2 steps, 1 chair, more than 1 chair). Fractures were categorized as cervical, trochanteric, and subtrochanteric, according to the The International Classification of Diseases, 9th Revision (ICD.9 code) in the medical record.

Bone Density Measurement

The BMD of the contralateral hip was measured by dual-energy X-ray absorptiometry within a week of having had the hip fracture. A Lunar DPX-L densitometer (version 4.6; Lunar, Madison, WI) was used for the first 42 subjects enrolled, and a Hologic QDR 4500 A densitometer (version 11.2.3; Hologic, Waltham, MA) was used for the remaining subjects. A cross-calibration formula based on 72 subjects, measured on both machines at the time of the switch, allowed the calculation of mean total hip BMD and total hip T-scores as if all subjects were measured on the Hologic machine. The cross-calibration formula was: total hip BMD Hologic (g/cm^2) = 0.968 (total hip BMD Lunar [g/cm^2]) – 0.031. Our laboratory's quality control protocol entails performing duplicate measurements once daily for all skeletal sites measured. The mean (SD) percent coefficient of variation (CV%) for the total hip is 1.00 (0.79)%, and for the femoral neck, it is 1.84 (1.25)%.

T-Score Calculation

For each subject, T-score at the total hip was calculated using first the NHANES and then the Lebanese database using the following formula: $T\text{-score} = (\text{subject's BMD} - \text{peak mean BMD}) / \text{SD of peak BMD}$. NHANES-based total hip T-scores were calculated based on information provided in the updated article describing the NHANES database (31,32):

$$\text{NHANES-based total hip T-score for women} = \frac{\text{subject's BMD} - 0.942}{0.122}$$

$$\text{NHANES-based total hip T-score for men} = \frac{\text{subject's BMD} - 1.04}{0.144}$$

For Lebanese-based total hip T-scores, mean peak BMD was derived from a population-based sample of subjects aged 25–35 yr, as reported previously (20).

Based on the WHO BMD-based operational definition of osteoporosis (33), subjects with a T-score ≤ -2.5 were considered to have osteoporosis.

Statistical Methods

Results are expressed as means \pm SD or as proportions, and analysis was conducted for the total sample and stratified by gender. Cases and controls were compared using parametric and nonparametric tests, as appropriate: the 2-tailed Student's *t*-test and Mann-Whitney *U*-test for continuous variables, and the chi-squared test and Fisher's exact tests for categorical variables. Logistic regression analysis was performed to examine the association between hip fracture and BMD, and results were expressed as OR (95% CI) per SD decrease in total hip BMD derived for the NHANES and the Lebanese database, first unadjusted and then adjusted for age and BMI. Similarly, ORs and their 95% CIs for hip fracture per SD decrease in BMI were estimated for the total sample and by gender. To examine whether effect measures varied by gender, we formed product terms of gender and BMD/BMI and used likelihood ratio tests to determine the significance of the interaction effects. All statistical calculations were performed using SPSS version 13.0 software (SPSS Inc, Chicago, IL). Differences were considered significant for $p < 0.05$.

Results

Clinical Characteristics

The average age of hip fracture subjects was 74 yr (9.4)—41 females and 19 males. Compared with controls, hip fracture subjects were significantly taller and had a lower BMI in the overall group and in subgroup analyses by gender (Table 1). Patients were more likely to be on calcium, vitamin D, or osteoporosis medications and to take sleeping pills or anxiolytic drugs (Table 1). Hip fractures occurred in the early afternoon, and mean reported time for their occurrence was 13.5 h (5.2). The anatomical distributions for hip fractures were as follows: 52% in trochanteric region, 38% in the

femoral neck, and 10% in the subtrochanteric area, with similar distribution between the left and the right hip (data not shown).

Fall Characteristics

The fractures were reported to have occurred with a fall that took place while walking (49%), changing positions (27%), sitting or standing (20%), or other positions (4%). These falls occurred with a slip (39%), a trip (29%), a bathroom slip (7%), or other reasons, and the reported fall direction was sideways (51%), backward (27%), forward (7%), or straight down (15%). The fall was reported as occurring from a standing height (59%), from 1 step or more (25%), a seated position (11%), or from bed (5%).

Bone Mineral Density T-Scores of the Total Hip and Prevalence of Osteopenia/Osteoporosis

Hip fracture subjects had a significantly lower mean (total hip) BMD than controls, in the overall group and by gender (Table 2). The proportion of subjects with osteoporosis was significantly higher in patients than controls, regardless of the database used, but was higher using the NHANES as opposed to the Lebanese database. Subgroup analyses by gender yielded similar results (Table 2). Patients with trochanteric fractures were older than those with femoral neck fractures— 76.2 ± 9 yr vs 71.2 ± 9 yr; $p = 0.045$. But the mean BMD at the total hip, femoral neck, and trochanter were, however, similar in both groups (data not shown).

Discriminate and Receiver operating characteristic (ROC) curve analysis for detecting patients with hip fractures using a T-score ≤ -2.5 and using either the NHANES or the Lebanese database, revealed that a sensitivity for picking up patients with hip fractures in the overall group was 45% using the NHANES database compared with 25% with the Lebanese database. Conversely, specificity was slightly larger when using the Lebanese database (87%) than the NHANES database (80%). Comparable results were obtained with subgroup analyses by gender (data not shown). Efficiency was overall slightly better on using the NHANES database (0.66) compared with the Lebanese database (0.62), whereas area under the curve estimates were quite comparable between the 2.

Estimates for Fracture Risk Based on Bone Mineral Density: Odds Ratio/Standard Deviation Decrease in Bone Mineral Density

Table 3 details the gradient of risk for fracture expressed as OR per SD decrease in total hip BMD derived using the NHANES and the Lebanese database for defining SD, first unadjusted, and then adjusted for age and BMI, in the overall group and by gender. For each SD decrease in BMD, fracture risk increased by 2.1-fold in the overall group—1.69 in women and 4.28 in men—using the NHANES database ($p = 0.039$ between genders). Comparable risk estimates were obtained on using the Lebanese database (Table 3). Adjusting for age and BMI estimates yielded similar results in the overall group and by gender.

Table 1
Clinical Characteristics of Patients with Hip Fracture and Controls (Mean \pm SD or Proportions)

Characteristics	Overall group			Women			Men		
	Patients (n = 60)	Controls (n = 90)	<i>p</i> Value ^a	Patients (n = 41)	Controls (n = 55)	<i>p</i> Value ^a	Patients (n = 19)	Controls (n = 35)	<i>p</i> Value ^a
Anthropometric									
Age (yr)	74 \pm 9.4	73 \pm 9	—	74 \pm 9.6	72 \pm 8.8	—	75 \pm 9.3	75 \pm 9.2	—
Height (cm)	161 \pm 8	154 \pm 9	0.001	158 \pm 6	149 \pm 6	0.001	168 \pm 7	162 \pm 7	0.004
Weight (kg)	70 \pm 11	70 \pm 13	—	70 \pm 10	68 \pm 12	—	71 \pm 13	73 \pm 14	—
BMI (kg/m ²)	27 \pm 4.3	30 \pm 5.5	0.005	28 \pm 4.0	31 \pm 5.7	0.020	25 \pm 4.2	28 \pm 4.6	0.016
Lifestyle (%)									
Smoking	27	28	—	24	29	—	32	26	—
Alcohol	22	16	—	20	11	—	26	23	—
Clinical (% on)									
Calcium pills	52	17	0.001	50	24	0.018	56	6	0.001
Vitamin D pills	36	8	0.001	23	13	—	56	0	0.001
Multivitamin pills	33	1	0.001	35	2	0.001	31	0	0.001
Sleeping pills	32	7	0.001	34	7	0.002	26	6	0.045
Anxiolytic pills	27	6	0.001	29	9	0.010	21	0	0.012
Osteoporotic medicine	51	4	0.001	50	7	0.001	53	0	0.001
Sleeping or anxiolytic pills	40	9	0.001	44	11	0.001	32	6	0.017

Abbr: SD, standard deviation; BMI, body mass index.

^aNot significant.

Estimates for Fracture Risk Based on Body Mass Index: Odds Ratio/Standard Deviation Decrease in Body Mass Index

Table 4 details the gradient of risk for fracture, expressed as OR per SD decrease in BMI, first unadjusted, and then adjusted for age, BMD, in the overall group and by gender. The OR was significant for BMI: 1.67 (1.16–2.40) for the overall group, 1.69 (1.07–2.66) for females, and 2.23 (1.05–4.74) for males, with no gender differences. The BMI remained significant while adjusting for age, gender, and for both variables. When BMD was added to the model, the ORs decreased and no significance was detected.

Discussion

This study investigated clinical and densitometric risk factors of hip fractures in Lebanese subjects. The derived fracture risk estimates using the aforementioned risk factors were comparable to those published in western populations, and most importantly, risk estimates derived from BMD, an important risk factor in the WHO global fracture risk assessment model, were very close to similarly derived estimates in western subjects. The use of the NHANES BMD database was superior to the use of a local database in identifying patients with fractures.

The mean age of Lebanese patients who recently sustained a first hip fracture was smaller, averaging 74 yr, and is consistent with ages we reported in a retrospective study at our institution (35), with reports from Kuwait and Iran (4,5), and with the large

Mediterranean Osteoporosis Study (MEDOS) study (36). This is in contrast to an older mean reported age ranging from 79 to 83.8 yr from other western countries (8,11–13). This may, in part, reflect the relatively old age cutoff for entry into these prospective cohorts (65 yr for Study of Osteoporotic Fractures (SOF) and 75 yr for The epidemiology of osteoporosis study (EPIDOS)). Conversely, the younger age in Lebanese patients with hip fractures may reflect their relatively shorter life expectancy at birth of 70 yr compared with western counterparts (37). Alternatively, it may be a reflection of the lower BMD in the Lebanese across all age groups (20,34), thus leading to fractures at a younger age for the same BMD (8). Hip fracture subjects were taller and had a lower BMI than controls, as reported in previous studies (38). The taller-stature association with hip fractures (38) may be explained by the longer hip axis length, a risk factor for hip fractures (9). The age- and gender-adjusted OR for hip fracture per SD decrease in BMI of 1.82 (1.23–2.69) is similar to that reported by Greenspan et al, that is, 2.2 (1.2–3.8) (38). The protective effect of BMI on fracture risk may be explained by the positive correlation between BMI and BMD, as its effect did not persist after adjusting for BMD in our study in contrast to results from the adjusted analyses of Greenspan et al (38).

Fall characteristics and the impact of sleeping pills and anxiolytics on hip fractures were similar to those described in previous reports (8,38). These clinical findings again underscore the importance of incorporating fall-prevention measures and the need to minimize the use of neuropsychotropic drugs as key public health precautions to prevent hip fractures in the elderly.

Table 3
OR for Hip Fracture per SD Decrease in Total Hip BMD

	Overall group		Women		Men	
	OR	95% CI	OR	95% CI	OR	95% CI
Unadjusted						
NHANES database	2.10	1.45–3.05	1.69	1.13–2.53	4.28	1.67–10.97
Lebanese database	1.85	1.35–2.55	1.53	1.10–2.14	4.55	1.71–12.13
Adjusted for age						
NHANES database	2.30	1.53–3.48	1.73	1.10–2.74	5.31	1.87–15.08
Lebanese database	1.98	1.40–2.81	1.57	1.08–2.28	5.70	1.92–16.88
Adjusted for age and BMI						
NHANES database	2.11	1.36–3.27	1.48	0.87–2.50	4.63	1.60–13.39
Lebanese database	1.83	1.26–2.65	1.38	0.90–2.12	4.94	1.64–14.92

For OR derived using the NHANES database, the difference between the OR derived for women and men is significant with $p = 0.039$ and the difference between the age- and BMI-adjusted OR derived for women and men is of borderline significance with $p = 0.071$.

For OR derived using the Lebanese database, the difference between the OR derived for women and men is significant with $p = 0.039$ and the difference between the age- and BMI-adjusted OR derived for women and men is significant with $p = 0.039$.

Abbr: OR, odds ratio; SD, standard deviation; BMD, bone mineral density; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.

women compared with men. This gender difference needs to be further investigated in larger cohorts.

Our study has limitations including its cross-sectional nature, its relatively small sample size, the fact that it is not population-based, drawbacks in general and for discriminate ROC analyses in particular, and did not include a systematic evaluation of all clinical risk factors included in FRAX (43). This was because the study had started before the availability of detailed information on the FRAX model. Nevertheless, it is, to our knowledge, the first of its kind providing insight into the impact of BMD and clinical risk factors on hip fracture risk in subjects from the Middle East. It also investigated the implications of differing database selection on patient diagnosis, and validated the international recommendation for universal database selection.

Lebanese subjects with fracture are relatively young, and BMD-derived risk estimates, such as those included in the FRAX model, also apply to the Lebanese. This study validates the use of a universal (NHANES) database and the applicability of risk estimates used in the WHO global fracture risk assessment model in the Lebanese.

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Table 4
OR for Hip Fracture per SD Decrease in BMI, Unadjusted and Adjusted for Age, for Total Hip BMD, for Gender, and for All Variables

	Overall group		Women		Men	
	OR	95% CI	OR	95% CI	OR	95% CI
Unadjusted ^a	1.67	1.16–2.40	1.69	1.07–2.66	2.23	1.05–4.74
Adjusted for age ^a	1.65	1.14–2.39	1.67	1.06–2.64	2.23	1.05–4.74
Adjusted for BMD ^a	1.28	0.85–1.92	1.36	0.81–2.29	1.50	0.66–3.42
Adjusted for gender	1.83	1.24–2.70				
Adjusted for age and gender	1.82	1.23–2.69				
Adjusted for age and BMD ^a	1.25	0.82–1.88	1.37	0.80–2.33	1.41	0.63–3.18
Adjusted for age, gender, and BMD	1.33	0.86–2.07				

Abbr: OR, odds ratio; SD, standard deviation; BMI, body mass index; BMD, bone mineral density; CI, confidence interval.

^aThe difference in OR between the 2 genders is not significant.

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