Osteoporos Int (2003) 14: 929–940
DOI 10.1007/s00198-003-1458-4

ORIGINAL ARTICLE

Prevalence of osteoporosis and its reproductive risk factors among Jordanian women: a cross-sectional study

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Received: 26 August 2002 / Accepted: 23 June 2003 / Published online: 7 October 2003

Abstract Extensive differences in the osteoporosis epidemiological pattern among geographic and ethnic groups have been reported. The evidence concerning association of multiple pregnancies, lactations, and other menstrual history factors with low bone mineral density (BMD) remains inconclusive. Previous local studies addressing these issues in Jordan are very restricted. We present a cross-sectional study of Jordanian women who visited outpatient clinics between August 2000 and August 2002 at two community hospitals in Amman City. BMD measurement was performed for all subjects, while comprehensive appraisal of clinical issues related to reproductive status and past medical history was carried out using a structured questionnaire administered to 50% of the subjects. We also attempted to examine the current hypothesis of possible influence of hyperlipidemia and thyroid abnormalities on decreased BMD. According to WHO criteria, 119 (29.6%) were identified as having osteoporosis, 176 (43.8%) were osteopenic, and 107 (26.6%) had normal BMD. The multiple-linear regression analyses at different bone sites revealed that age, years of menopause, low-density lipoprotein (LDL), and follicle-stimulating hormone (FSH) have strong independent associations with decreased BMD at all lumbar and femoral neck regions. The negative effect associated with number of children (live births) and frequency of lactations was only evident at femoral neck. Although years of menstruation, age at menopause, days of menstrual cycle, number of pregnancies, and duration of hormone replacement therapy (HRT) were positively correlated with BMD, they had weaker associations than previous variables. Moreover, in the final multivariable logistic regression model, variables which rendered significantly independent risk factors after adjustment for age and BMI were: current smokers of more that 25 cigarettes/day, postmenopausal women irrespective of HRT use, menopausal years of ≥5 year intervals, natural early menopause, gastrointestinal disease, rheumatoid arthritis, osteoarthritis, hypertension, and thyroid replacement therapy. Ever-lactation, frequent lactation of 4 or more times, duration of lactation interval of 1–6 months and clinical hyperthyroidism were significant protective factors. Hysterectomy with or without oophorectomy, premature ovarian failure, gravidity, menstrual flow pattern, family history of osteoporosis, clinical hypothyroidism, hyperlipidemia, HRT, and corticosteroids therapy were not independent predictors of osteoporosis among our population. It was concluded that the prevalence of this worldwide public health problem among the Jordanian female population is extremely high, and is even found in younger age categories compared to previous international surveys. Though, the number of pregnancies in our multiparous female population showed a negative impact on femoral neck BMD, no evidence of increased risk of osteoporosis among ever-pregnant women was noted. Conversely, the current data analysis highlight many potential risk factors including associated medical illnesses, and other hormonal alterations experienced during menopausal period. Therefore, increased health awareness and intensive screening programs are mandatory for early detection of low bone mass.

Keywords Epidemiology · Jordan · Menopause
Osteopenia · Osteoporosis · Risk factors · Women

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Introduction

Unless prevented or actively treated, osteoporosis will continue to limit both the quantity and quality of life for many older women and significantly add to the health care costs of this rapidly growing population group worldwide

[1, 2]. However, extensive differences in the epidemiological pattern of hip fracture among geographic regions, ethnic groups, races, and gender have been reported [1, 2, 3, 4]. Moreover, according to several epidemiologic projections published over recent years, specific regions such as Asia, Latin America, the Middle East and Africa will account for over 70% of all fractures in the world by the year 2050 [5, 6, 7]. According to the Jordan Department of Statistics, women of age 50 and older are estimated to be 4.5% of the 1994 Jordanian population and is estimated to increase to 6% in the year 2009 [8].

As osteoporosis is a ''silent disease'', dual-energy X-ray absorptiometry (DXA) is widely used for diagnostic measurement of bone mineral density (BMD) [9, 10]. However, recognition of various artifacts and pathologic processes that can falsely increase the measured BMD is essential to accurate DXA scan analysis [11]. Critical evaluation of the DXA scan image, and careful appraisal of numeric data on the computer-generated printout by clinicians and radiology technologists are instrumental to ensure correct DXA scan interpretation. Therefore, sets of laboratory biomedical markers for bone resorption and bone formation were suggested to resolve the uncertainty of diagnosis [12, 13]. Moreover, in an attempt to guide the bone densitometry measurements, several international epidemiological surveys in different parts of the world have extensively analyzed potential osteoporosis risk factors, including demographic and social information, personal medical history, maternal and paternal history of bone fracture after age of 50 years, smoking habit, alcoholic beverage consumption, calcium intake and present and past physical activities [14, 15, 16, 17, 18, 19, 20, 21]. Conclusions obtained from these studies were controversial according to various ethnic groups. Therefore, extrapolation of these findings to our population and implementation in our routine clinical evaluation is not necessarily valid. In particular, factors such as menstrual, obstetric and lactation history, and their long term effect on BMD in postmenopausal period have not been intensively analyzed or described in a multiparous women population, such as Jordan. Previous international publications on these issues suggest that premenopausal amenorrhea [22] is a potential risk factor for low postmenopausal BMD, as well as loss of maternal minerals during pregnancy and lactation [23, 24, 25, 26, 27, 28]. Subsequent-lactation BMD recovery was demonstrated by 6 or 12 months postpartum, depending on the lactation period. However, the results from these studies were inconsistent, although available prospective and clinical data have unequivocal opinions in terms of increasing or decreasing osteoporosis and osteopenia incidence that may occur later in life in women who have had multiple pregnancies and lactations [29, 30, 31].

In Jordan, the number of studies that addressed the problem of osteoporosis among the Jordanian population is very limited. In fact, only two epidemiological studies have been conducted at two different medical centers [32, 33]. The population of the first study was perimenopausal women only, while the second study included men and women regardless of menopausal condition. The former survey was prospectively conducted, while the latter study involved a retrospective analysis of medical records for specific hip fracture cases. Both studies focused on one aim, which was to evaluate associated factors with low bone mineral density and/or fracture. These issues included demographic variables (age, weight) and simple clinical variables (such as gender, menopause, medication history). In addition, the protocol of previous studies did not involve collection of blood samples. Therefore, evaluation of hormones, lipid profiles, 24-h urinary calcium excretion, and serum vitamin D were not detected.

Therefore, we set out to conduct a large-scale project with the aim of achieving the following tasks: to determine the risk factors associated with development of osteoporosis in Jordanian society (400 patients); to evaluate the significance of recent biomedical markers of bone formation and bone resorption for diagnosis of osteoporosis and monitoring of anti-osteoporotic treatment (120 patients); to examine whether early changes in biomedical markers predict long-term changes in bone mineral density (BMD) in elderly women (120 patients); and to evaluate the efficacy and safety of one of the biphosphonates (Alendronate) for prevention and treatment of osteoporosis in Jordanian women (120 patients).

The current paper will address the cross-sectional epidemiological part of the study, which was concerned with assessing the potential risk factors associated with low BMD in our female population, with special emphasis on maternal and reproductive history variables. Details of the epidemiological pattern of osteopenia and osteoporosis and their associations with social variables and other potential medical illnesses can be found elsewhere [84].

Materials and methods

Study design and subjects

A prospective cross-sectional survey was conducted at two major health centers, one located in the east region (Al-Bashear Hospital) and another in the west region (Ibn-Al-Haytham Hospital) of Amman city, the capital of Jordan. The former center is a public sector and provides medical services for a population of lower socioeconomic status than the latter center, which is private sector. The study was conducted from 2000 to 2002. Initially, 200 female subjects were consecutively recruited while visiting primary health clinics at the two centers. An additional 200 women were enrolled through a random telephone survey, so as to achieve a final sample of women that was more representative of the general Jordanian population. Pregnancy and lactation were the only exclusion criteria. BMD measurement was performed for all subjects, while physical examination, structured-questionnaire interviewing, as well as blood and urine samples were obtained from approximately 50% of those who agreed to be involved in the full protocol of the study. No significant differences in mean age and anthropometric measures were observed between subjects who received interview and examination and those who did not. Women were classified

according to reproductive status into pre-, peri-, and postmenopause, based on previously defined criteria [34, 35]. The local research ethics committee approved the study protocol and all volunteers gave written informed consent.

Measurement of BMD

BMD measurements were carried out using the Lunar DPXL DXA densitometer (Lunar, Madison, Wisc., USA). Daily-standardized measurement of a Lunar phantom and Hologic Anatomic spine phantom served as quality control for the bone densitometer. The coefficient of variation (CV) of the technique at our institution was 0.8%, using a phantom measured 3 times a week during the 2-year period of the current prospective study. Measurements at both the lumbar spine [AP: L2–L4 (LS)] and femoral hip (neck, wards, trochanter) were made. BMD was expressed in g/cm^2. We used Spanish femur and spine reference population for young women based on the age range 20–40 years. *T*-Scores were calculated using the standard formula as follows: *T*-score = BMD of participant mean−mean BMD of reference population/SD of BMD of reference population. Cut-off values to categorize individuals as having low bone mass (osteopenia) or osteoporosis utilized the WHO criteria [36], so that osteoporosis was defined as a *T*-score of less than –2.5 SD. Osteopenia denoted a *T*-score of –1 to –2.5 SD. The software also provided a *Z*-score of BMD, which is obtained by comparison to reference mean matched for sex, age and weight. Therefore, a *Z*-score value of –1 SD or less was considered to show severe osteoporosis at increased risk of fracture [37, 38, 39, 40]. Licensed technicians who had completed training by the manufacturer of the densitometer they were using conducted all testing. Two experienced radiologists at each center further confirmed diagnosis.

Laboratory measurements

A 24-h urine collection and fasting blood samples were obtained during the day before interview. Blood samples were centrifuged immediately, separated, and stored at −20°C until all measurements were completed.

Glucose, total cholesterol, triglycerides (TG) and high density lipoprotein cholesterol (HDL) were determined in the fasting blood samples by standard enzymatic-colorimetric methods, while low density lipoprotein (LDL) was estimated by calculation using the Friedewald formula [41]. TSH, FSH and FT4 were assayed by using standard enzyme immunoassay commercial kits. Total serum calcium (Ca), serum creatinine (Cr), and serum albumin were determined by standard chemistry kits (Chiron Diagnostics, Ceba). Calcium corrected for albumin (Ca) was obtained according to the following formula: corrected Ca = total calcium (mg/dl) + 0.8 [4−serum albumin (g/dl)] [42, 43]. The normal reference range is (8.2–10.2 mg/dl). Twenty-four-hour urinary Ca and Cr were estimated in the whole collected urine volume throughout the day. The purpose of creatinine measurement is to ensure that the urine has been adequately and completely collected for the full 24 h. The normal ranges of urinary Ca and Cr excretions were 0.1–0.3 g/24 h and 1–2 g/24 h, respectively. Calcium excretion of less than 100 mg over 24 h almost always indicates a vitamin D deficiency. Excretion of more than 250 mg in 24 h may indicate an excess renal loss of calcium [45]. Creatinine clearance (CrCl) was further calculated to test the kidney function based on standard equations [43].

Questionnaire interviewing and definitions of risk factors

Potential risk factors for osteoporosis employed in this study were identified from the medical literature [14, 15, 16, 17, 18, 19, 20, 21, 44, 45, 46]. The questionnaire included 50 items in the following six sections: social history, physical examination, past medical history, reproductive history, family history of osteoporosis, and drug history. The research coordinator administered the questionnaire to all subjects on a face-to-face basis. Social history included physical activity, marital, educational, socioeconomic, and smoking status. Physical examination involved checking for height loss, kyphosis, scoliosis, abnormal gait, bowing of the long bones, bone deformity, hyporeflexia and signs of rheumatoid arthritis [46]. In addition, systolic/diastolic blood pressure and anthropometric variables (height, weight, waist and hip) were measured by qualified nursing staff. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Past medical history involved ascertainment of previous history and duration of peptic ulcer, malabsorption, rheumatoid arthritis, renal insufficiency, systemic hypertension, diabetes mellitus, angina, dyslipidemia, malignancy, myocardial infarction and any cardiovascular disease. Reproductive history included both obstetric and menstrual history. Women were classified as nulliparous or as having had one or two births, three births, and four or more births. Lactation period was defined as the time during which the mother provided two-thirds of the required energy intake per kg of infant weight by breastfeeding [47]. Times and duration of lactation duration during each time were obtained. Participants were subsequently grouped according to average duration of lactation into: none to < 1 month, 1–6 months, and more than 6 months. Menstrual history included age at menarche and at menopause, regularity of menstruation before menopause (regular, irregular, too frequent, and absent), duration of menstrual period (days), menstrual flow (heavy, light, or normal), and whether the women's periods ceased naturally, or if hysterectomized whether one or both ovaries were preserved. For medication history, women were questioned whether they had ever used the following therapy, which are known to affect BMD [46], and for how long: corticosteroids, non-steroidal anti-inflammatory drugs, anticonvulsant agents, thyroid replacement therapy, aluminum-containing antacids, immunosuppressive agents, heparin, and hormone replacement therapy (HRT). Women were classified according to their response to this item into: never-users, ever-users, and current-users.

Statistical analysis

Statistical analysis was performed using SPSS (version 10) statistical software package. All descriptive variables are expressed as mean (standard deviation, SD). The analysis of the variance (ANOVA) and multiple regression analysis were used, as appropriate. Multiple linear regression analyses were carried out to investigate associations between continuous variable and BMD at different femoral and lumbar bone sites. A *P*-value of < 0.05 (two sided) was used to denote statistical significance, though associations reaching borderline significance ($0.05 < P < 0.1$) were also identified as being of potential interest.

The odds ratio (OR) of osteoporosis was then estimated in a multivariable logistic regression model, and ORs and their 95% confidence intervals (95% CI) are presented. All potential risk factors, whether or not they demonstrated significant associations with BMD in univariate analysis were included in an initial model, and backward stepwise elimination was used to arrive at the final model. Goodness of fit was evaluated using the Hosmer-Lemeshow statistic.

Results

Table 1 displays the general population characteristics. Among the total sample size of 400 Jordanian women who underwent BMD measurements, the mean age was 53.23 years and ranged between 19 and 85. According to WHO criteria, 119 (29.6%) were identified as having osteoporosis, 176 (43.8%) were osteopenic, and 107

Table 1 General characteristics of the study population

Variable	Mean (SE), median
Age (years)	53.23 (0.6), 53
Height (cm)	156.6 (0.35), 157
Weight (kg)	75.1 (0.7), 74
BMI (kg/m^2)	30.7 (0.3), 30
H/W ratio	0.88 (0.01), 0.86
BMD femoral neck (g/cm^2)	1.02 (0.009), 0.998
BMD lumbar spine (g/cm^2)	0.85 (0.007), 0.85
Ever-pregnant [*n* (%)]	185 (91%)
No. of pregnancies	6 (0.3), 6
Ever-breastfed [*n* (%)]	176 (86.7%)
Duration of lactation (months)	9.2 (0.5), 8

(26.6%) had normal BMD. With regard to menopausal status, of the 204 subjects who were interviewed 41 (20.1%) were premenopause, 29 (14.2%), perimenopause, and 134 (65.7%) postmenopause. Current or past estrogen use was reported by 20% and current or past cigarette smoking by 31%.

Table 2 shows the distribution of BMD diagnostic categories based on *T*-score by anthropometry, reproductive variables, and drug history. A significant difference in mean age was verified among the subgroups, with the oldest age women (57.6 ± 9.3) being represented in the osteoporosis group, while the youngest female (48.5 ± 9.3) was in the normal BMD category (ANOVA test, $P < 0.00$). With further stratification of subjects based on their ages into 5-year intervals, the highest prevalence of osteopenia (16.4%) and osteoporosis (11.7%) was demonstrated in the 50–59 years age category (Chi-square test, $P < 0.000$).

With regard to reproductive history, postmenopausal women were more likely to develop osteoporosis and osteopenia in contrast to pre and perimenopausal subjects (Chi-square test, $P < 0.000$). With further stratification analysis of postmenopausal women condition, hysterectomised women, or those who had additional bilateral oophorectomy, and women whom their menopause was due to premature ovarian failure (< 35 years old) or natural early menopause (< 45 years old) were not more likely to develop osteopenia or osteoporosis as compared with women of normal menopause ($P > 0.05$). Additionally, the age of menopause did not fluctuate significantly between normal and reduced BMD subgroups (ANOVA test, $P = 0.5$). However, number of years since menopause was higher in osteoporotic women as compared to normal or even osteopenic women (ANOVA test, $P = 0.001$ and 0.02, respectively). With regard to gravidity, there were no significant differences in the prevalence of osteoporosis and osteopenia between ever-pregnant and never-pregnant women (Chi-square test, $P = 0.78$). With further stratified analysis based on number of children, there were no significant associations between number of live births and osteopenia or osteoporosis (Chi-square test, $P = 0.48$). Interestingly, the initial comparison showed no significant associations between lactation status (yes versus no; Chi-square test, $P = 0.2$), or number of lactation times (ANOVA test, $P = 0.35$) and neither osteoporosis nor osteopenia prevalence. However, stratification analysis revealed statistically significant elevation in osteoporosis and osteopenia among women of extensive lactation period for 6 months or more as compared to women with 1–6 months or 0–1 month lactation intervals (Chi-square test, $P = 0.043$). Concerning menstrual history, no significant associations were found between age at menarche, years of menstruation, days of period, or menstrual flow pattern and the existence of osteopenia or osteoporosis (data shown in Table 1).

Surprisingly, women who reported a positive family history of osteoporosis or recalled loss of height (> 2 inches) among one or more of their first degree relatives were not more likely to develop osteoporosis as compared with women with a negative family history (Chi-square test, $P = 0.13$).

With respect to medication history, the prevalence of osteoporosis and osteopenia was significantly high among women who had indicated current or previous use of calcium supplements, bisphosphonates, or calcitonin as compared to never-users. Their physicians mainly attributed this to their previous history of low bone mass that required proposition of these medications. Moreover, in this sample a total of 40 (20%) women reported utilization of HRT for a mean of 23 ± 37 months; however, the overall protective effect of HRT was not robustly demonstrated in the present data (Chi-square test, $P = 0.39$). Yet, when further stratified analysis was carried out, findings obtained suggested that current-users of HRT were less likely to develop osteoporosis as compared to ever-, and never-users groups in our study (Chi-square test, $P = 0.042$). Interestingly, the duration of HRT use seemed to play a role in the results observed, since mean duration differed significantly among the three diagnostic groups (ANOVA test, $P = 0.04$), with the highest mean being reported in the normal group (12.6 ± 33 months), followed by osteopenic (6.5 ± 21), and lastly by osteoporotic groups (1.9 ± 8.2). Surprisingly, subjects who had ever used corticosteroids ($n = 22$, 10.8%) were not significantly more likely to develop osteoporosis compared to never-users in the same sample (Chi-square test, $P = 0.87$). Conversely, thyroid replacement-users were significantly more likely to be exposed for osteoporosis (Chi-square test, $P = 0.01$) in contrast to non-users. Other medications known to induce decreased bone mass, such as aspirin, NSAIDs, heparin and aluminum antacids, did not prove significant impact on the size of osteoporosis or osteopenia in our population, despite their long-term use (i.e. NSAIS, 36.3 ± 56 months).

Multiple linear regression analyses

Multiple-linear regression models were constructed separately for each of the following bone site: lumbar Spine (L1, L2, L3, L4, L2–L4) and femoral (neck, wards,

Table 2 Prevalence of BMD diagnostic categories based on *T*-score (at any site) is given by anthropometry, reproductive variables and medication history.*BMD* bone mineral density

Variables	Normal (NV)	Osteopenic (OPN)	Osteoporotic (OPO)	*P*-value*	*P*-value**
No. of subjects (%)	107 (26.6)	176 (43.8)	119 (29.6)	–	–
BMD femoral neck (g/cm^2)	0.99 ± 0.1	0.85 ± 0.08	0.72 ± 0.1	–	0.000 +
BMD lumbar spine (g/cm^2)	1.24 ± 0.12	1.02 ± 0.08	0.84 ± 0.103	–	0.000 +
T-score femoral neck	0.13 ± 0.85	−1.1 ± 0.714	−2.1 ± 0.898	–	0.000 +
T-score lumbar spine	0.33 ± 0.99	−1.47 ± 0.74	−2.93 ± 0.83	–	0.000 +
Age (years, mean ± SD)	48.5 ± 9.3	53.1 ± 10.5	57.6 ± 9.3	–	0.000 +
Anthropometry					
Height	159 ± 5.9	156.9 ± 6.2	154 ± 7	–	0.000 +
Weight	80 ± 14.5	75.2 ± 13.3	70.5 ± 12.6	–	0.000 +
BMI (kg/m^2)	31.7 ± 5.6	30.7 ± 5.9	29.7 ± 4.9	–	0.044 +
Waist/hip ratio	0.85 ± 0.08	0.88 ± 0.12	0.87 ± 0.09	–	0.232
Reproductive history					
Premenopause	19 (46.3)	57 (42.5)	58 (43.3)	–	–
Perimenopause	11 (37.9)	15 (51.7)	3 (10.3)	–	–
Postmenopause	19 (14.2)	57 (42.5)	58 (43.3)	–	–
Hysterectomy	4 (19)	12 (57.1)	5 (23.8)	0.474	0.163
Oophorectomy	3 (4.29)	4 (57.1)	0 (0)	0.188	–
Premature ovarian failure (< 35 years)	2 (28.6)	3 (42.9)	2 (28.6)	0.958	0.323
Natural early menopause (< 45 years)	5 (11.6)	16 (37.2)	22 (55.2)	0.081	–
Age of menopause	49 ± 6.12	47.8 ± 5.5	47.9 ± 5.9	–	0.588
Menopausal years	6.1 ± 6.4	8.8 ± 7.5	12 ± 8	–	0.001 +
Gravidity	45 (24.3)	83 (44.9)	57 (30.8)	0.778	–
Nulliparous	4 (23.5)	6 (35.3)	7 (41.2)	0.479	–
1–2 births	0 (0)	6 (66.7)	3 (33.3)	–	–
3 births	3 (37.5)	2 (25)	3 (37.5)	–	–
4 or more births	42 (24.9)	76 (45)	51 (30.2)	–	–
Lactation	42 (23.9)	82 (46.6)	52 (29.5)	0.201	–
1–2 times	2 (11.8)	10 (58.8)	5 (29.4)	0.006	0.348
3 times	7 (46.7)	8 (53.3)	0 (0)	–	–
4 or more times	33 (22.9)	65 (45.1)	46 (31.9)	–	–
Average duration of lactation	7.6 ± 7	9.4 ± 6	9.9 ± 8	–	0.232
0 to < 1 month	10 (28.6)	9.(25.7)	16 (45.7)	0.043	–
1–6 months	14 (26.9)	28 (53.8)	10 (19.2)	–	–
> 6 months	25 (21.7)	53 (46.1)	37 (32.2)	–	–
Menstrual history					
Age at menarche	12.9 ± 1.6	13.3 ± 1.5	13.5 ± 1.6	–	0.162
Years of menstruation	36.4 ± 6.4	34.7 ± 5.4	34.5 ± 6.2	–	0.320
Regular	41 (23.6)	75 (43)	58 (33.3)	0.080	–
Irregular	5 (22.7)	13 (59)	4 (18.2)	–	–
Too frequent	3 (75)	1 (25)	0 (0)	–	–
Days of period	5.9 ± 1.8	5.7 ± 1.7	5.7 ± 1.5	–	0.715
Menstrual flow					
Heavy	19 (29.2)	26 (40)	20 (30.8)	0.685	–
Light	2 (14.3)	8 (57)	4 (28.6)	–	–
Normal	27 (22.5)	55 (45.8)	38 (31.7)	–	–
Family history of osteoporosis					
Yes	18 (23)	39 (50)	21 (26.9)	0.130	–
No	29 (29)	37 (37)	34 (34)	–	–
Unknown	2 (8.7)	14 (60.9)	7 (30.4)	–	–
Loss of height (> 2 inches)	12 (18.2)	33 (50)	21 (31.8)	0.557	–
Medication history					
Aspirin	10 (32.3)	11 (35.5)	10(32.3)	0.454	–
NSAIS	22 (27.2)	35 (43.2)	24 (29.6)	0.704	0.667
HRT	11 (27.5)	20 (50)	9 (22.5)	0.390	–
Never-users	38 (23.3)	70 (42.9)	55 (33.7)	0.024	–

*Asymptotic significance (two-sided) for Pearson Chi-Square test
**ANOVA test for the difference among subgroups means (for categorical variables, it represent years of exposure to the variable)
+The mean difference is significant at the 0.05 level

troch). All analyses were adjusted for age, W/H ratio, BMI and variables of interest. Standard coefficients (estimates), standard errors (SE), and significance levels of all terms selected for multiple regression analyses are presented in Table 3.

The results for different lumbar and femoral bone sites were frequently consistent among the included variables. Age and years of menopause were found to have strong negative independent associations with all lumbar and femoral neck BMDs (g/cm^2), although non-

Table 3 Predictors of BMD (g/cm^2) at different sites: Results from multiple-linear regression analyses

Variables	Lumbar spine (L2–L4) estimate[a] (SE), *P*-value	Femoral neck estimate[a] (SE), *P*-value
Age	−0.004 (0.002), 0.016	−0.004 (0.001), 0.001
W/H ratio	0.193 (0.348), 0.581	−0.339 (0.250), 0.179
BMI	0.008 (0.002), 0.001	0.009 (0.002), 0.000
Height	0.009 (0.002), 0.000	0.007 (0.002), 0.000
Weight	0.004 (0.001), 0.000	0.004 (0.001), 0.000
Years of menstruation	−0.019 (0.075), 0.8	0.011 (0.061), 0.863
Years of menopause	−0.028 (0.011), 0.013	−0.037 (0.010), 0.000
Years of hysterectomy	0.088 (0.054), 0.104	−0.023 (0.039), 0.564
Age at menopause	0.001 (0.008), 0.887	0.001 (0.007), 0.861
Duration of HRT (months)	0.022 (0.032), 0.490	0.003 (0.022), 0.214
Days of menstruation	0.005 (0.009), 0.622	0.006 (0.007), 0.460
Average duration of lactation	0.003 (0.041), 0.936	0.047 (0.031), 0.135
No. of pregnancies	0.003 (0.01), 0.769	0.003 (0.008), 0.673
No. of children	0.009 (0.015), 0.549	−0.008 (0.003), 0.013
No. of lactations	−0.015 (0.011), 0.177	−0.007 (0.003), 0.027
Total cholesterol	−0.346 (1.028), 0.737	−0.485 (0.755), 0.522
Triglycerides	−0.311 (0.191), 0.106	−0.071 (0.143), 0.623
HDL	−0.003 (0.007), 0.713	−0.043 (0.019), 0.023
LDL	−0.194 (0.093), 0.039	−0.206 (0.066), 0.002
FBS	0.041 (0.097), 0.676	0.051 (0.073), 0.488
Total cholesterol/HDL ratio	1.901 (1.464), 0.197	1.293 (1.104), 0.244
LDL/HDL ratio	1.525 (1.006), 0.132	1.335 (0.725), 0.068
Thyroid function tests		
TSH	−0.014 (0.033), 0.685	−0.013 (0.025), 0.597
FT4	0.055 (0.049), 0.267	0.026 (0.037), 0.490
FSH	−0.697 (0.341), 0.043	−0.007 (0.003), 0.031
Total serum calcium	0.014 (0.015), 0.361	−0.009 (0.012), 0.423
Serum creatinine	0.136 (0.156), 0.387	−0.042 (0.120), 0.731
24-h urinary calcium	−0.023 (0.032), 0.484	−0.041 (0.025), 0.104
Creatinine clearance	1.4 (0.000), 0.034	0.001 (0.000), 0.037

[a]The parameter estimate indicates the estimated change in BMD per unit increase in the explanatory variable

significant associations with femoral wards and troch BMDs were observed. Intriguingly, of the remaining reproductive variables, the number of children (live births) and number of lactations had persistent negative independent associations with BMD; these were statistically significant for femoral neck ($P = 0.02$), weakly negative for lumbar spine, but non-significant for femoral troch and wards. Unexpectedly, W/H ratio, duration of HRT use, years of menstruation and years of hysterectomy were not considered associated with BMD at any site ($P > 0.1$).

With regard to laboratory measurements, creatinine clearance was established to have robust positive independent associations with lumbar spine and femoral neck BMDs. However, there were no significant associations between thyroid function tests (TSH, FT4), FBS, total serum calcium or 24-h urinary calcium excretion and BMD results. FSH serum level had strong negative associations with BMD at lumbar spine and femoral sites. These changes in FSH level appear to correlate with onset of menopause or decline in estrogen concentrations, leading to increased bone loss. Moreover, though the total cholesterol was negatively related with femoral wards and troch (data not shown), these results were of borderline significance ($0.05 < P < 0.1$) and were not observed at any other site. However, of the remaining lipid components, both HDL and LDL had strong negative impact on BMD, particularly at femoral neck.

Multiple logistic regression analyses

The ORs and 95% CIs for the final multivariable logistic regression model, with *T*-score of –2.5 or lower as the dependent variable, are displayed in Fig. 1. The effect of advancing age was independent of all other factors, with odds of osteoporosis for women aged 50 years or older of 7.27 times (95% CI, 2.68–19.74) higher than women aged below 50 years.

Social variables significantly associated with increased risk of osteoporosis in the final stepwise logistic model were primary school education (OR, 0.12; 95% CI, 0.02–0.74) and current smoking of more than 25 cigarettes/day (OR, 19.01; 95% CI, 1.41–256.9). Women who reported slight and heavy physical activity had increased odds of osteoporosis compared with those who had sedentary lifestyle (OR, 5.6; 95% CI, 0.74–43.02 and OR, 2.4; 95% CI, 0.11–50.9, respectively), though these estimates did not attain the level of statistical significance. On the other hand, women who reported moderate physical activity were significantly less likely to develop osteoporosis (OR, 0.04; 95% CI, 0.002–0.76; $P = 0.03$).

During the physical examination, positive findings of kyphosis (OR, 3.78; 95% CI, 1.22–11.7), bowing of long bones (OR, 3.4; 95% CI, 0.98–11.5), loss of height (OR, 2.4; 95% CI, 1.001–5.54), balance problem (OR, 3.4; 95% CI, 1.2–10.14) and non-traumatic fracture (OR, 21; 95% CI, 1.5-292.5) were associated with increased odds

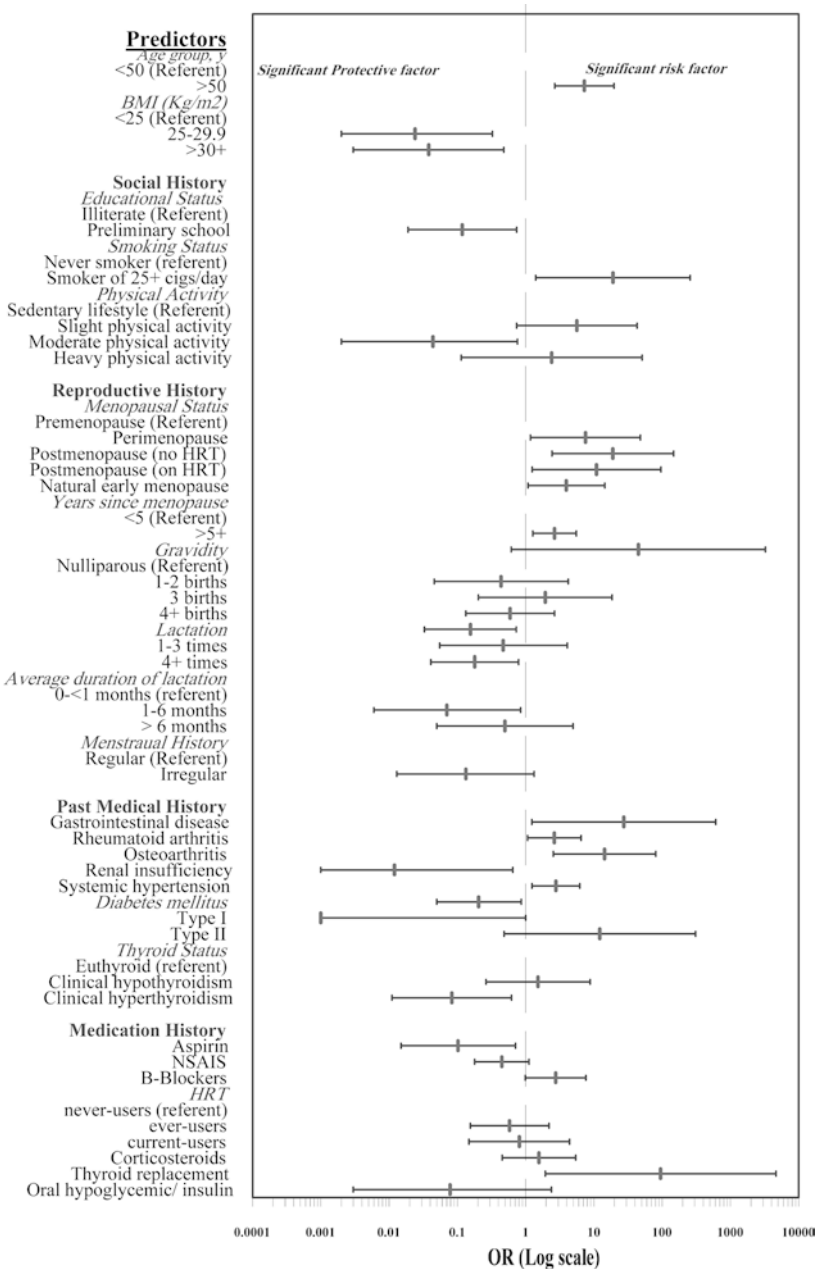

Fig. 1 Predictors of osteoporosis (T-score < –2.5) obtained by multiple logistic regression analysis. The results are represented as odds ratios (OR) and their 95% confidence intervals

of osteoporosis. However, positive findings of scoliosis (OR, 0.79; 95% CI, 0.23–2.76) and traumatic fracture (OR, 2.9; 95% CI, 0–4.5) were insignificant predictors of osteoporosis.

With respect to reproductive history, the final model revealed that perimenopausal and postmenopausal women who did not receive HRT were 7.5 (95% CI, 1.2–48, $P = 0.03$) and 19 times (95% CI, 2.4–147.6, $P = 0.005$) more likely to have osteoporosis compared to premenopausal women. Postmenopausal women who used HRT were still at higher risk for osteoporosis than normal menstruating women (OR, 10.9; 95% CI, 1.25–95.9; $P = 0.03$). As was shown in the previous linear regression section, number of years since menopause was related to significantly greater odds of osteoporosis, independent of age, particularly if greater than 5 years since menopause. Among the postmenopausal group, women who underwent hysterectomy (OR, 0.75; 95% CI, 0.17–3.4) and/ or oophorectomy (OR, 0.001; 95% CI, 0.0001–3.4) were more likely to be protected from osteoporosis, though these findings did not attain the level of statistical significance. Women who had natural early menopause were significantly at higher likelihood of osteoporosis (OR, 13.98; 95% CI, 2.6-73), while those who had premature ovarian failure were not (OR, 0.6; 95% CI, 0.04–7.4). Further, the final stepwise logistic regression analysis disclosed that periods of lactation, of whatever number or duration, were a significant independent protective factor (OR, 0.16; 95% CI, 0.03–0.7), particularly in women who had lactated four or more times (OR, 0.16; 95% CI, 0.03–0.84), and if the average duration of lactation was in the range of 1–6 months

(OR, 0.07; 95% CI, 0.006–0.85). Gravidity, menstrual regularity, menstrual flow, and family history of osteoporosis failed to arrive at the significance level required to be included in the final logistic model.

With regard to past medical history, significant predictors that established increased osteoporosis risk were gastrointestinal disease (OR, 27.5; 95% CI, 1.24–609.8), rheumatoid arthritis (OR, 2.6; 95% CI, 1.07–6.5), osteoarthritis (OR, 14.3; 95% CI, 2.5–80.4) and hypertension (OR, 2.8; 95% CI, 1.24–6.2), while other encountered diseases such as type I diabetes (OR, 0.21; 95% CI, 0.05–0.86; $P = 0.03$) and renal insufficiency (OR, 0.012; 95% CI, 0.05–0.65), were associated with decreased probability of osteoporosis. Interestingly, clinical hyperthyroidism was observed to be a significant independent protective factor (OR, 0.08; 95% CI, 0.011–0.62), while other thyroid illnesses were not related to the likelihood of osteoporosis in the present data analysis. The remaining medical problems, including hyperlipidemia, type II diabetes, angina and coronary artery disease, were dropped from the model due to weak associations.

Discussion

The current survey is the largest study of female osteoporosis conducted in Jordan. The overall rate of osteoporosis of 30% among all the Jordanian women involved in this study (irrespective of menopausal status), and its prevalence of 43.3% among postmenopausal women are striking figures compared to previously published international studies. The general magnitude in these studies has varied between 3.5% and 16% [20, 49, 50, 51]. In the USA, a recent example is the NORA study [20], which reported an osteoporosis incidence rate of 7% among the entire sample of 200160 postmenopausal women. However, our estimations are more in agreement with previous local surveys [32, 37, 48]. For postmenopausal women who aged between 50 and 59 years old in our study, the magnitude of osteoporosis and osteopenia was 31% and 43.7%, while the corresponding rates obtained from the previous Jordanian experiences ranged between 13%–28% and 40%–46%, respectively.

The inclusion of 400 women of wide range of ages composing various menopausal conditions allowed us to evaluate the independent significance of age, menstrual, parity, and associated medical factors as predictors of bone mineral density. In addition, performing DXA scanning at more than one skeletal site for all patients allowed more accuracy and precision in BMD measurements and reduced the chance of missing a diagnosis of low bone mass. Particularly in patients over 65 years old, increased degenerative or hypertrophic changes will sometimes falsely elevate the spine BMD if measured in the PA direction by DXA [52]. Therefore, the potential utility of direct hip as well as peripheral densitometry in this age group is greater than for those in early menopause.

The present study confirmed that age over 50 years, and years in menopause are still the most important risk factors for predicting femoral and lumbar BMD in women, even after adjusting for other variables such as BMI, weight, and HRT use.

Particularly with regard to years in menopause, the increased risk was evident in 6–10 years and over 35 years intervals. The question of whether a significant lag time of reduced BMD exists during the peak of the climacteric period, with manifestations of hot flushes and other unwanted effects associated with cessation of estrogen at the beginning of menopause, and whether the loss of BMD was regained later in life due to disappearance of these manifestations, remains to be resolved in a future prospective follow-up study.

Moreover, previous longitudinal follow-up studies [53, 54, 55] have demonstrated accelerated bone occurring during the perimenopausal phase; with the highest annual rate of bone loss in perimenopausal women, intermediate in postmenopausal women, and lowest in premenopausal subjects. In contrast, our data showed that mean BMD measurement (g/cm^2) of lumbar spine (L2–L4) and femoral neck as well as their *T*-scores was not significantly different between perimenopause and premenopause periods (ANOVA test, $P > 0.7$). Yet, the corresponding BMD measurements were significantly lower in postmenopause compared to the previous two periods (ANOVA test, $P = 0.000$).

In a recent prospective study [60] of 38 women during their full-term pregnancy until 12 months postpartum, it was suggested that calcium needed for fetal skeletal growth during pregnancy was gained from maternal trabecular and cortical sites and that needed for infant growth during lactation was drawn mainly from the maternal trabecular skeleton [23, 24, 25, 26, 27, 28, 29, 30, 31]. Our results demonstrated that women who had ever lactated, particularly those who reported four or more lactations, were less likely to develop osteoporosis than their non-lactating counterparts. However, lactation for more than 6 months duration was associated with increased risk of osteoporosis compared to less extended periods of breastfeeding. These findings have led to the speculation that frequent lactation is essential for remodeling of bone by increasing resorption and subsequent formation postpartum and during breastfeeding. However, women should be recommended not to extend the lactation period for more than 6 months, and in addition to adopt a more calcium-rich diet to support the rebuilding of their bones. The mechanisms, which are involved in the promotion of bone health recovery during and subsequent to that period of life need to be further investigated in prospective studies.

The evidence as to whether hysterectomy with or without additional oophorectomy is related to decreased BMD remains inconclusive [61, 62, 63, 64, 65, 66, 67]. Three previous studies [61, 62, 64] have found that hysterectomized women had a higher BMD than non-hysterectomized women, whether or not their ovaries had been removed or conserved, and this association

was independent of HRT use. In contrast, two other studies [63, 65] concluded that undergoing hysterectomy induced reduction in BMD, whereas two more surveys [66, 67] observed no significant impact of these operations. In the present study, among postmenopausal women who had hysterectomy (10.4%), oophorectomy (3.5%), or premature ovarian failure (3.5%), their estimated odds ratio of osteoporosis indicated less risk than their counterparts. However, the low prevalence of these events in this cross-sectional study may have resulted in wider 95% confidence intervals, indicating statistical non-significance. Moreover, though the quantitative regression displayed inconsistent negative impact of years since hysterectomy on femur BMDs and positive effect on vertebral BMDs, the correlation estimates did not reach the level of statistical significance. Therefore, it is premature to state unequivocally that hysterectomy is associated with beneficial influence on BMD. In our view so far, the conclusion drawn from current data are more consistent with findings of the latter two studies [66, 67] demonstrating no association between the suggested variables. Therefore, further wider-scale investigations with more emphasis on hysterectomized women are required to clarify these issues.

A particular point of interest is that in the present analyses, we were able to quantify the direct linear effect of available continuous anthropometric, reproductive, and laboratory variables on BMDs at different bone sites, which are most commonly submitted to examination by DXA densitometers worldwide. The multiple-linear regression analyses section provided strong evidence for independent negative influence of age and years since menopause on femoral neck and most lumbar bone sites, while the negative impact of prolonged lactation period was only evident on some lumbar sites. Although years of menstruation, average days of menstrual cycle, age of menopause, and body surface area were significantly associated with increased BMD in separately fitted models (data not shown), the final multivariate adjusted model revealed their non-statistical implication. Interestingly, duration of HRT use and years of hysterectomy were even considered of less impact compared to previously mentioned variables on BMD at various sites when included in the same linear models. Therefore, they were often dropped from the model, revealing less independent association with BMD at any site. Except for menstruation years, these findings are consistent with several recently published reports [61, 68, 69, 70]. Moreover, unlike a previous study [16], we found a strong independent association between number of pregnancies and decreased femoral neck BMD, but no significant effect on other sites. However, we were more cautious about drawing any conclusion when no further evidence of association between ever-pregnancy and development of osteoporosis was drawn from the multiple logistic regression analysis. It was therefore concluded that despite the continuous reduction of BMD on femoral neck with frequent pregnancy, it was not likely to be an independent risk factor for subsequent incidence of osteoporosis in our multiparous female population.

The physiological normal bone growth development during childhood and puberty is very crucial in determining of bone mass and bone density in adults [13]. This process is dependent on numerous hormonal factors like growth hormone and sex steroids levels [19]. Several investigators [22, 71, 72, 73] reported lower vertebral BMD in young females who experienced oligomenorrhea/amenorrhea as compared with normal menstruating peers. This was primarily attributed to the prolonged hypoestrogenic state associated with unlimited interruptions in the normal menstrual cycle. The observation of lower BMD was limited to the spine and was not seen in the femoral neck. However, more recent data suggested that higher BMI might override the negative influence of hypoestrogenic state [22]. The observed interaction between menstrual pattern, body weight, and vertebral density were illustrated by three possible explanations: body weight is distinctive for body size, therefore larger women have a higher bone mass; body weight is the workload in weight-bearing exercise, and the skeleton responds to the greater mechanical stress by boosting mass; and there is an enhanced conversion of androgens to estrone in the adipose tissue of heavier women. In fact, Buchanan et al. [74] recently reported no relationship between the level of estrone and vertebral bone density ($r = 0.19$) in 30 young women of similar weight. The present study seemed to support this hypothesis. Our current data suggest that menstrual regularity and flow pattern were not significant predictors of low BMD in our population. These observations could be related to the increased body weight (mean, 75.1) and BMI (mean, 30.7) noted among the majority of included women in our study sample.

Another possible hypothesis for the influence of plasma lipoprotein and other hormonal disturbances on bone metabolism has also been examined. With regard to lipid parameters drawn from our population, the inverse correlation between HDL or total cholesterol and vertebral BMD is consistent with previous studies [75, 76, 77] which suggested an interesting as yet unexplained association between these parameters in postmenopausal women. Nevertheless, these findings emphasized the importance of screening metabolic factors that could influence the bone health in absence of hormonal regulation. Moreover, our preliminary observation of LDL strong negative impact on BMD has lent further support to recently presented data in a basic pharmacological study [81] which suggested that LDL oxidation products promoted osteoporotic bone loss in murine marrow stromal cells. However, our final estimations of odds ratio are not compatible with the hypothesis [79, 80] that hyperlipidemia decreases BMD in human subjects and thereby increases the risk of osteoporotic fractures.

Despite many studies, confusion still exists regarding the effect of thyroid hormone on skeletal health [81, 82, 83]. The effect of thyroid hormone on skeletal integrity is

thought to be mediated through hyperthyroidism, exogenous or endogenous suppression of thyroid-stimulating hormone (TSH), and thyroid replacement therapy [81]. Overall, systemic overviews of cross-sectional studies, longitudinal studies, and meta-analyses found that hyperthyroidism and use of thyroid hormone to suppress TSH because of thyroid cancer, goiters, or nodules seemed to adversely affect the cortical bone, particularly in postmenopausal women. Our data support the deleterious effect of thyroid replacement therapy on bone, with increased odds ratio of osteoporosis in women who had been using thyroxine compared to those who did not. However, the negative association of hyperthyroidism with osteoporosis prevalence in our population may be explained by the rapid altering of thyroid gland function and other disease states associated with these illnesses [81].

Several clinical trials [56, 57] and observational studies [58] have highlighted the efficacy of HRT for reduction of bone loss and prevention of fracture following menopause. Yet, although 20% of our sample reported employment of HRT, the rigorous appraisal of our data demonstrated a beneficial impact on BMD only in current users. These findings were in agreement with a previous study [59] in peri- and postmenopausal women, which revealed that once supplemental estrogen is withdrawn, rapid bone loss results, especially if the duration of use was less than 10 years [58, 59]. Consequently, within a few years, the BMD of women who received HRT is no different from that of women who did not receive it.

Collectively, the present comprehensive study, which evaluated various risk factors, may provide a solid basis on which to develop standards of disease recognition and strategies for treatment and prevention.

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