

The Effect of Vitamin D Deficiency, Premenopausal Hysterectomy with or without Oophorectomy, and Other Demographic Factors on the Risk of Osteoporosis in Postmenopausal Women

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Abstract

Background: Osteoporosis (OS) poses significant risks to postmenopausal women, leading to debilitating fractures and reduced quality of life. This bone disease, characterized by diminished bone mass and strength, is influenced by age, genetics, ethnicity, and hormonal changes, profoundly impacting the susceptibility to fractures in older women. **Aim of the Study:** The aim of this study was to evaluate the effect of certain demographic factors such as duration of menopause, premenopausal hysterectomy, Vitamin D deficiency, and other factors on bone mass reduction and OS occurrence. **Patients and Methods:** This cross-sectional study was conducted at Baghdad Teaching Hospital from January to October 2023 and involved 150 postmenopausal women aged 45–65 years. To assess bone health, data were gathered through questionnaires, physical examinations, and laboratory tests, including dual X-ray absorptiometry (DEXA) scans and Vitamin D levels. **Results:** Out of 150 postmenopausal women studied, 58% had OS, and 42% did not have Osteoporosis (NOS). Risk factors for OS included age, obesity, smoking, lack of physical activity, and menopause duration over 5 years. Hysterectomy with oophorectomy significantly increased OS risk. Vitamin D deficiency correlated strongly with OS. Low serum calcium and Vitamin D levels emerged as independent predictors of OS, with reduced serum calcium linked to a 7.8-fold increased risk. **Conclusion:** The study revealed a high prevalence of OS (58%) among postmenopausal women. Key risk factors include aging, higher body mass index, smoking, inactivity, and prolonged menopause. OS risk is notably higher posthysterectomy with oophorectomy. Vitamin D deficiency and low serum calcium are significant, independent predictors of OS.

Keywords: Hysterectomy, oophorectomy, osteoporosis, postmenopausal, Vitamin D

INTRODUCTION

Osteoporosis (OS), a standard bone disease in humans, poses a greater risk to older individuals more susceptible to osteoporotic fractures. These fractures can have a profound impact on quality of life, causing disability, loss of independence, institutionalization, and increased mortality. Understanding the full extent of these consequences can help us empathize with those affected.^[1]

Primary OS refers to the loss of bone brought on by age and low estrogen levels after menopause. After menopause, estrogen levels start to decline, losing their ability to control bone resorption. Because of this, bone resorption occurs more quickly and is typically not offset by the production of new

bone. In the early postmenopausal years, the rate of bone loss is at its fastest.^[2] Secondary OS is the term used to describe OS caused by other conditions or drugs.^[2]

Vitamin D controls calcium metabolism, making it essential for healthy bones. It is crucial to bone health, especially in postmenopausal women. Calcium, a vital bone mineral,

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must be retained for solid bones. Vitamin D helps the body absorb calcium from food for bone formation.^[3] Numerous studies have shown that Vitamin D is important for bone health in menopausal women. Calcium homeostasis and bone health require Vitamin D. In postmenopausal women, Vitamin D deficiency lowers bone density and increases fracture risk.^[4] Different studies examine the complex relationship between Vitamin D, menopause, and aging. Vitamin D deficiency, common in postmenopausal women, can cause OS.^[5]

However, hysterectomies may increase the risk of OS and bone fractures. Hysterectomy increased OS and bone fracture risk by 2.2-fold after 6 years. Several studies show that premenopausal hysterectomy without oophorectomy can cause premature ovarian failure and a 1-year drop in Anti-müllerian hormone AMH. Premenopausal oophorectomy causes immediate surgical menopause and OS. Postmenopausal hysterectomy plus oophorectomy increases fracture risk compared to the predicted fracture rate because ovary-generated androgen may reduce fracture incidence.^[6]

This study aimed to evaluate the effect of certain demographic factors such as duration of menopause, hysterectomy, Vitamin D deficiency, and other factors on bone mass reduction and OS.

PATIENTS AND METHODS

This cross-sectional study was conducted in the Department of Obstetrics and Gynecology at Baghdad Teaching Hospital from January 1, 2023, till the end of October 2023. The study included 150 postmenopausal women between 45 and 65 years old. Verbal consent was obtained from each patient before collecting data. All information is kept confidential in a password-secured laptop, and data are used exclusively for research purposes. Administrative approvals were granted by the Scientific Council of Obstetrics and Gynecology/Iraqi Board for Medical Specialization and the Department of Obstetrics and Gynecology at Baghdad Teaching Hospital.

The study included postmenopausal women and women with a history of hysterectomy with or without bilateral oophorectomy more than 1 year ago. It excluded chronic drug users (statin, corticosteroid, hormones, and diuretics for more than 3 months), women on regular calcium and Vitamin D supplements, and women with other medical conditions that cause OS (malignancy, Diabetes mellitus (DM), thyroid and parathyroid disorders, Chronic kidney disease (CKD), and inflammatory arthritis).

The sample was collected from Baghdad Teaching Hospital's consultation gynaecology clinic. Staff paramedics at the hospital and their family members agreed to participate in the study after being fully informed. Verbal consent was obtained from each patient before data collection. Data were collected using a well-designed questionnaire that covered various aspects as the following:

Demographic data included age, educational level, occupation, age at menopause or hysterectomy, and other relevant demographic characteristics. Past medical history included information related to OS, such as previous diagnoses of OS or fractures, factors associated with increased risk of Vitamin D deficiency, and medical diseases that cause OS. Surgical history included a hysterectomy with or without an oophorectomy, its duration, and indications (benign or malignant). Social history included risk factors for Vitamin D deficiency, including limited sun exposure, use of sun protection measures, dark skin tone, and dietary habits. There is also a history of OS or OS-related fractures in first-degree relatives. Drug history included any drugs that cause OS or are used to treat it and any supplement used for its prevention.

Participants underwent a comprehensive general examination using a mechanical scale, including anthropometric, height, and weight measurements. Participants were instructed to stand still and upright without lifting additional weight, ensuring consistent measurement techniques. Body mass index (BMI) was taken from the weight and height measurements using the same scale for all participants. BMI was calculated by dividing weight in kilograms by the square of height in meters. The definition of overweight was a BMI greater or equal to 25 kg/m²; obesity was a BMI ≥ 30 kg/m².^[7]

Laboratory analysis was conducted to assess various biomarkers related to bone health and Vitamin D levels:

- Serum calcium and albumin levels: These were measured to estimate corrected calcium levels
- Serum Vitamin D levels: Five milliliters of venous blood were withdrawn from each participant and underwent centrifugation for 10 min at 3000 RPM. The serum was mixed with the reagent (25-OH Vitamin D, catalog number G5-6832/R03B5P020, Abbott). After a few minutes, the mixture was introduced into a spectrophotometer (Abbott i1000SR) to measure Vitamin D levels in ng/ml. The reference range provided by the manufacturer for Vitamin D levels was 30–80 ng/ml
- Serum alkaline phosphatase levels: This biomarker was measured to indicate bone turnover
- General investigations: Complete blood count, Thyroid function test (TFT), renal function tests, and liver function tests were performed to evaluate overall health and identify potential confounding factors.

The radiology department used a DEXA scan (Excellus, OsteoSys) to measure the participants' bone mineral density. The DEXA scan focused on measuring the lumbar spine T-scores (the lumbar vertebrae contain primarily trabecular bone, an important diagnostic criterion for OS). A T-score < -2.5 is considered essential for the diagnosis.

All data were introduced into Microsoft Excel 16, and statistical analysis was conducted using IBM Corp. Released 2007. IBM SPSS Statistics for Windows, Version 16.0. Armonk, NY: IBM Corp. Data were presented in the form of counts, percentages, mean, standard deviation, minimum (min), and maximum (max)

in tables, charts, or graphs. The categorical data's significance level was tested using the Chi-square or Fisher's exact test. In contrast, continuous variables were tested using the Student *t*-test or Mann–Whitney *U* test when appropriate. -To find the best cutoff points, the Youden's J index test was used along with the receiver operator characteristic (ROC) curve. The area under the curve, sensitivity (SN), specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy of the test (Acc), and relative risk of each variable were all estimated.

RESULTS

One hundred and fifty postmenopausal women were enrolled in the study. According to the result of the DEXA scan, cases were divided into two groups: the OS group, 87 (58%) cases, and the no OS (NOS) group, 63 (42%) cases. Table 1 shows that the risk of OS goes up significantly with age, being overweight or obese, smoking, not being active, and having been through menopause for more than 5 years.

Patients who underwent hysterectomy with oophorectomy had significantly higher rates of OS than those without oophorectomy or with no surgical history. Cases of hysterectomy alone are also significantly higher than cases with no surgical history, as shown in Table 2.

As Table 3 shows, the longer the duration since hysterectomy, the higher the rate of OS.

Vitamin D deficiency was significantly associated with cases of OS, with $P < 0.0001$. The univariate analysis of investigations and their relation to OS showed that low serum calcium, low Vitamin D, high serum alkaline phosphatase, and high serum creatinine were associated with OS. The application of multivariate analysis (to eliminate the effect of other factors) showed that serum calcium and Vitamin D were independent predictors of OS. Furthermore, every unit reduction in serum calcium is associated with a 7.8 times increased risk of OS, as shown in Table 4.

For OS prediction, variables significantly associated with OS were further analyzed using ROC curve analysis. Serum calcium and Vitamin D were low in cases of OS and found to be fairly sensitive in the prediction of OS. Both were not specific, but both had excellent NPV, making them good tests for ruling out OS. On the other hand, BMI was not sensitive but highly specific for OS, and a BMI of more than 31.1 kg/m² was associated with a high PPV of 84.8%, making it a good predictor of OS, as shown in Table 5.

DISCUSSION

OS is a common illness that significantly affects the health of women who have gone through menopause. OS is more common as people age, especially after menopause, when estrogen levels are dropping. Age, genetic susceptibility, early menopause, fracture history, slender build, and lifestyle

Table 1: Distribution of patient's demographics according to the presence of osteoporosis

Variables	OS, n (%)	NOS, n (%)	Total, n (%)	OR	P
Age group (years)					
45–49	9 (10.3)	18 (28.6)	27 (18)	1	0.002
50–54	29 (33.3)	26 (41.3)	55 (36.7)	2.23	
≥55	49 (56.3)	19 (30.2)	68 (45.3)	5.16	
BMI group (kg/m ²)					
18.5–24.9	19 (21.8)	23 (36.5)	42 (28)	1	0.039
25–29.9	28 (32.2)	23 (36.5)	51 (34)	1.47	
≥30	40 (46)	17 (27)	57 (38)	2.85	
Smoking					
Yes	19 (21.8)	5 (7.9)	24 (16)	3.24	0.022
No	68 (78.2)	58 (92.1)	126 (84)	0.31	
Physical activity					
Active	6 (6.9)	19 (30.2)	25 (16.7)	0.17	0.021
Inactive	81 (93.1)	44 (69.8)	125 (83.3)	5.88	
Duration of menopause (years)					
≤5	13 (14.9)	22 (34.9)	35 (23.3)	0.33	0.004
>5	74 (85.1)	41 (65.1)	115 (76.7)	3.03	

OS: Osteoporosis, NOS: No OS, OR: Odds ratio, BMI: Body mass index

Table 2: Past surgical history and its relation to osteoporosis

Variables	OS	NOS	OR	Past surgical history	P
Hysterectomy + BO (n=41)	37 (90.2)	4 (9.8)	14.15	Hysterectomy + BO versus TAH	0.035
Hysterectomy (n=23) without oophorectomy	16 (69.6)	7 (30.4)	3.5	Hysterectomy + BO versus no surgery	<0.0001
No surgery (n=86)	34 (39.5)	52 (60.5)	1	Hysterectomy versus no surgery	<0.0001

TAH: Total abdominal hysterectomy, BO: Bilateral oophorectomy, OR: Odds ratio, BMI: Body mass index, OS: Osteoporosis, NOS: No OS

variables such as smoking, low calcium diet, and insufficient physical exercise are essential risk factors.^[8] OS is a severe condition that progresses silently and has a high risk of fractures, which can result in significant morbidity and mortality. Hip and spine fractures can have a significant negative influence on a person's quality of life by causing chronic pain, incapacity, and reliance.^[9] Gynecologists must identify these risk factors in their postmenopausal patients as it is a severe health issue that needs to be addressed in this group, given the aging population and the corresponding rise in OS prevalence.^[10]

The rate of OS in the postmenopausal women in the current study was 58%. Using the WHO definition of OS, the disease affects approximately 21.2% of women over 50 years globally.^[11] In Saudi Arabia, a few studies have estimated the prevalence of OS among adults ranging from 23.4% to 39.5%.^[7] A study with a large sample ($n = 1079$) of Jordanian postmenopausal women aged between 45 and 84 years showed that the prevalence of OS was 37.5%.^[12] The pooled prevalence of OS in Iranian postmenopausal women was 33.70%.^[13] The prevalence of this variation of osteoporosis in postmenopausal women is influenced by several factors, including geographical distribution and dietary habits, as indicated by Dahl *et al.*^[14] This may also pertain to variations in sun exposure and the resultant Vitamin D synthesis, potentially influenced by the clothing choices of postmenopausal women, as indicated by Mohamed *et al.*^[15]

The study's results show that higher age is significantly associated with an increased rate of OS, as found in previous studies by Salari *et al.*,^[16] Lorentzon *et al.*,^[9] and Yong and Logan.^[17] Some researchers think this drop in bone mineral density in postmenopausal women is because they are making

less estrogen. Estrogen has receptors on osteoclasts that stop bone resorption when they are activated. This keeps bone density high. However, menopause causes this bone resorption inhibitory activity to go away, as suggested by Cheng *et al.*^[18]

The present study shows that the increase in BMI is associated with significant increases in the rate of OS; previous studies (Gkastaris *et al.*,^[19] Qiao *et al.*,^[9] and Pagnotti *et al.*^[20]) found similarly that obesity (high BMI) is associated with an increased rate of OS. Gkastaris *et al.*^[19] in their study suggested that obesity had both beneficial and harmful effects on bone mineral density; factors such as higher estrogen levels in obese postmenopausal women, complex effects of leptin and adiponectin on bone cells, and increased pro-inflammatory cytokines associated with obesity contribute to this intricate relationship. In addition, obesity leads to altered bone marrow adipogenesis, favoring fat cell formation over bone-forming cells, and lower Vitamin D levels, crucial for bone health. This complex interplay affects bone density and fracture risk, challenging the traditional view of obesity as protective against OS.

The result of the study shows that smoking was significantly associated with OS, a result similar to that of Weng *et al.*^[21] and Thomas *et al.*,^[20] who found that smoking had adverse effects on the osteoblastic activity of the bone, thus increasing the risk of OS.

This study shows that less physical activity and a sedentary lifestyle are linked to a higher risk of OS. This is similar to what Pinheiro *et al.*^[22], Marini *et al.*^[23], and Brooke Wavell *et al.*^[24] found Physical activity positively influences bone metabolism by adapting bones to mechanical loading, activating key signaling pathways promoting osteoblast formation, and inhibiting osteoclast activity. Regular exercise, particularly during critical growth periods such as childhood and adolescence, enhances bone density and strength, helping to delay the onset of OS. It achieves this by modulating inflammatory responses and hormonal levels, reducing oxidative stress, and maintaining a balance between bone formation and resorption. Consequently, exercise is a crucial nonpharmacological approach to improving bone health and preventing OS, as suggested by Faienza *et al.*^[25]

Table 3: Duration since hysterectomy

Variables	OS	NOS	OR	P
Duration since hysterectomy				
<5	6 (11.3)	4 (36.4)	0.22	0.038
5–10	33 (62.3)	7 (63.6)	4.5	
>10	14 (26.4)	0	-	

OS: Osteoporosis, NOS: No OS, OR: Odds ratio

Table 4: Distribution of investigations and relation to osteoporosis

Variables	OS, mean±SD	NOS, mean±SD	OR*	Univariate (P)	Multivariate (P)
Serum calcium	8.1±0.75	9.25±0.72	7.8	<0.0001	<0.0001
Serum albumin	4.07±0.43	3.95±0.41	1.04	0.110	0.956
Serum Vitamin D	14.07±4.81	24.28±5.92	1.42	<0.0001	<0.0001
Serum ALP	142.27±33.38	129.36±30.86	0.99	0.039	0.192
Blood urea	40.93±9.28	40.93±6.23	1	0.980	0.878
Serum creatinine	1.02±0.19	0.96±0.16	0.05	0.035	0.075
AST	41.08±14.58	42.34±13.48	1.03	0.517	0.171
ALT	34.38±11.46	34.82±10.39	1	0.836	0.970
T-score**	-2.97±0.31	-0.44±0.89	-	<0.0001	-

*OR calculated according to multivariate analysis (logistic regression analysis), **The T-score was excluded from the multivariate analysis as it is the defining variable of OS (the nonlinearity assumption was not met). OS: Osteoporosis, NOS: No OS, OR: Odds ratio, SD: Standard deviation, ALP: Alkaline phosphatase, AST: Aspartate transferase, ALT: Alanine transaminase

Table 5: Interpretation of receiver operator characteristic curve analysis

Predictors	Serum calcium	Vitamin D	BMI
The AUC	0.861	0.863	0.741
cutoff	9.25	21.95	31.1
SN	72.3	73.5	45.2
SP	54.9	56.9	90.2
PPV	72.3	73.5	84.8
NPV	93.3	96.7	57.5
Accuracy	58.7	60.0	64.9

BMI: Body mass index, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, SN: Sensitivity, SP: Specificity

Similar to what Fistarol *et al.* found, this study shows that the risk of OS goes up with the duration of menopause.^[26] This is probably related to the deficiency of estrogen, and the longer the duration since menopause, the longer the period of low estrogen exposure leads to a higher rate of OS.

The current study found that women who had a hysterectomy without an oophorectomy had a higher risk of osteoporosis, though not as high as women who had a bilateral oophorectomy. People who had a total abdominal hysterectomy without an oophorectomy were much more likely to have osteoporosis than people who had never had a hysterectomy. This finding suggested the presence of the role of the uterus in the dilemma of postmenopausal OS. Xu *et al.* found a negative impact of hysterectomy on ovarian function, which can lead to decreased ovarian reserve and follicular atresia, resulting in reduced long-term estrogen secretion. Estrogen is crucial for maintaining bone density, and its reduction accelerates bone mineral loss. Therefore, women who undergo hysterectomy experience a more significant gradual loss of bone mineral density compared to women with an intact uterus, increasing their risk of developing OS.^[27]

A low level of Vitamin D is associated with an increased rate of OS, with similar results found in multiple studies (De Martinis *et al.*,^[28] Romano *et al.*,^[29] and Polzonetti *et al.*^[30]). The mechanism associated with this increased risk is attributed to several factors: first, Vitamin D is essential for calcium absorption from the gut. Without sufficient Vitamin D, the body cannot absorb enough calcium, irrespective of the dietary intake. Calcium is vital for maintaining bone strength and density. Thus, a deficiency in Vitamin D can lead to lower calcium levels in the bones, weakening them and increasing the risk of OS, as suggested by Fleet.^[31] Vitamin D is necessary for bone mineralization, where minerals (such as calcium and phosphate) are deposited in bones to strengthen and harden them. A deficiency in Vitamin D disrupts this process, leading to softer, weaker bones and osteomalacia in adults, which can be a precursor to OS, as suggested by Jannin *et al.*^[32] Vitamin D deficiency can lead to an increase in parathyroid hormone (PTH) levels. Elevated PTH levels can result in bone resorption, where the body breaks down bone tissue to release calcium into the bloodstream. This process weakens the

bones, increasing the risk of OS, as Cheng *et al.*^[18] suggested. Vitamin D plays a role in the functioning of osteoblasts and osteoclasts. Deficiency in Vitamin D can disrupt the balance between these cells, leading to inadequate bone formation and increased bone breakdown, as suggested by van Driel *et al.*^[33]

Low serum calcium is associated with an increased rate of OS; this is probably due to the decreased availability of calcium for the mineralization of the bones. The multivariate analysis found that low serum calcium and Vitamin D are the independent predictors of OS. The current study found that serum calcium ≤ 9.25 is associated with 72.3% sensitivity in the prediction of OS in postmenopausal women, with a high NPV of 93.3%, suggesting that postmenopausal women with calcium levels above 9.25 are 93.3% less likely to be osteoporotic. This means checking serum calcium is a good way to rule out OS.

CONCLUSION

Fifty-eight percent of the women who had gone through menopause and were part of the study had OS. The risk of OS goes up a lot with age, a higher BMI, smoking, not being active, and menopause lasting more than 5–10 years. OS risk goes up a lot after a hysterectomy with oophorectomy. Low calcium levels in the blood and insufficient Vitamin D are independent signs of OS. A higher BMI is linked to a high PPV, which can help predict OS. Normal Serum calcium and serum vitamin D3. Vitamin D levels are linked to a high NPV, which can help rule out OS.

This research proposes that women at risk should undergo bone density scans and make lifestyle changes such as engaging in physical activity and consuming a diet rich in calcium and Vitamin D. It highlights the importance of providing care to women with hysterectomies. To enhance bone health in Iraq, the study suggests increasing awareness among healthcare professionals and advocating for collaboration with health ministries and organizations to establish screening protocols and management guidelines and launch educational campaigns. In addition, it emphasizes the need for studies throughout Iraq to investigate the prevalence, risk factors, and genetic and environmental influences on OS.

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Conflicts of interest

There are no conflicts of interest.

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