World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

Check for updates

Optimal dual calcium and cholecalciderol dosages for osteoporotic fracture risk patients

Khaled Mohammad Juma Husain Bani Hani [1,*], Sinan Ibrahim Alghamaz [1], Madher Ali Mohammad Doumi [1], Rami Mohamad Salem Aldarawshe [1], Suhib Fayiz Naim Dawaghreh [1], Ahmed Mahmoud Mohammed Ali Alboun [2] and Kholoud Muhsen Al Quraan [3]

[1] *Rehabilitation and rheumatology specialist, Royal Medical Services, Jordan.*
[2] *Registered Nurse, Royal Medical Services, Jordan.*
[3] *Lab Technician, Royal Medical Services, Jordan.*

World Journal of Biology Pharmacy and Health Sciences, 2024, 17(03), 205–220

Publication history: Received on 01 March 2024; revised on 20 March 2024; accepted on 22 March 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.17.3.0120

Abstract

Background: Vitamin D is crucial for musculoskeletal health, promoting calcium absorption, osteoid tissue mineralization, and muscle function. Insufficient levels can lead to bone dystrophy, muscle weakness, and osteoporotic fractures.

Aims: This research investigates the correlation between bone mineral density and osteoporotic fracture risk, including positive and negative influences, and aims to determine the optimal vitamin D level.

Methods: This retrospective observational study examined 206 Jordanian rehabilitation and rheumatology clinic patients from September to November 2021. The participants were post-menopausal women and men over 60. The Age-adjusted Charlson Co-Morbidity Index and Functionality Grade system was used to assess participants' co-morbidity burden and functionality. DEXA scans assessed participants' proximal femoral hip and anteroposterior spine. Participants were divided into two Vit D groups: those below 30 ng/ml and those above 30. Results were compared using a Chi Square test. The study examined correlations, total variations, and Vit D prediction quality using logistic regression analyses. SPSS 23.0 was used for statistical analysis with a 5% significance level.

Results: A binary logistic regression model was employed to simulate the correlation between the vitamin D levels of patients and their bone mineral density. The model indicated a 61.39% likelihood of having a fH_BMD (femoral head bone mineral density) equal to or greater than 0.755 g/cm2 when the vitamin D level is at its optimal value of 27.25 ng/ml. The model indicated a 27.25% likelihood of a fHOPF risk-free tool with a value of ≥3% when the optimal vitamin D level is 27.25 ng/ml. The model indicated a 17.74% likelihood of experiencing a significant osteoporotic fracture within the next 10 years.

Conclusion: The findings of our study demonstrated a direct correlation between elevated levels of vitamin D and improved bone mineral quality indices that were examined. The serum 25-OH Cholecalciferol levels are more likely to have a beneficial effect on bone health status.

Keywords: Bisphosphonate; Vertebral fracture; Non-Vertebral fracture; Optimal threshold; Osteoporosis

* Corresponding author: Khaled Mohammad Juma Husain Bani Hani1*,

1. Introduction

An increase in the risk of fractures and a decrease in bone mass density (BMD) are two of the defining characteristics of osteoporosis. This condition is most prevalent in women aged 60 and older and in men aged 70 and older. For women, the average lifetime likelihood of experiencing at least one episode of osteoporotic fracture is approximately 40–50%, while for men, the likelihood ranges from 13-22%. This is specifically for western countries. According to the statistics, approximately fifty percent of women and twenty percent of men who are fifty years old or older will suffer at least one osteoporotic fracture during the course of their remaining lifespan. [1-3]

Patients who are elderly and have experienced a fracture as a result of osteoporosis will be provided with long-term care. This type of care is frequently accompanied by a decline in quality of life as well as negative consequences such as decreased functionality, increased burden of co-morbidities, and higher mortality rates. Hip fractures are the most severe type of fracture that can be caused by osteoporosis. They are also associated with a mortality rate of approximately thirty percent within one year of the fracture occurring. It is important to note that hip fractures are particularly dangerous. [3-5]

The presence of vitamin D is necessary for a wide range of physiological processes that contribute to the overall health of our musculoskeletal system. The mineralization of osteoid tissue, the optimisation of muscle function, and the absorption of calcium and phosphorus are some of the functions that are included in this complex, interconnected, and interdependent set of functions. Bone dystrophy and muscle weakness are symptoms that are associated with secondary hyperparathyroidism. [6-8]

These symptoms can be brought on by a deficiency of serum 25-OH cholecalciferol, which is the primary form of vitamin D that is found in the bloodstream. Furthermore, the presence of this deficiency raises the probability of experiencing osteoporotic fractures over the course of one's lifetime. There is a strong correlation between the serum vitamin D level and the nutritional status of affected patients over the long term. [9-11]

There are some findings that are controversial regarding the clinical effects of vitamin D levels on the quality of bone microarchitecture; however, the majority of studies indicate that there are significant positive associations between vitamin D levels and bone mineral content and density (BMC and BMD), bone diameter and size in relation to body size, bone strength and quality, and overall bone compactness and resistance to fractures. [12-15]

There are not many studies that have compared multiple outcomes of interest with serum vitamin D levels within a single study. This is a significant gap in previous research. The primary purpose of this research was to investigate the specific relationships that exist between the bone mineral densities of the femoral hip and the lumbar spine, as well as the incidence of femoral and overall major osteoporotic fractures over the course of a decade. For the purpose of analysing these associations, the levels of serum 25-OH-Cholecalciferol in patients who were receiving treatment at our institutional rehabilitation clinic were taken into consideration.

2. Material and methods

This study trial was a retrospective observational study that involved 206 participants who received treatment at our rehabilitation and rheumatology clinic between September 2021 and November 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan. The study was conducted in Jordan.

Participants in this study were not allowed to participate if they had a history of metabolic osteodystrophy, either renal or non-renal, documented vertebral or non-vertebral anatomical malformities or osteoporotic fractures, or metabolic or non-metabolic secondary osteoporosis, including bone metastasis related to cancer. In this particular study, the participants were restricted to women who had reached menopause and men who were at least sixty years old.

Data regarding the co-morbidity burden and functionality statuses of patients were collected from the assessment notes of the participants. These notes were collected from the patients. The Age-adjusted Charlson Co-Morbidity Index (AACCI) and the Functionality Grade system were utilised, respectively, in order to accomplish the aforementioned assessment goals. The data obtained from dual-emission X-ray absorptiometry (DEXA) scans of the proximal femoral hip and the anteroposterior spine were obtained from the DEXA database that was recorded.

The database that is associated with DEXA includes a variety of measurements and scores that are associated with bone density and fracture risk measures. These include the femoral Hip T-Score (fHip T-Score), the femoral Hip Z-Score (fHip

Z-Score), the femoral Hip Body Mass Index (BMD) in grammes per square centimeter (fH_BMD), the Lumbar T-Score, the Lumbar Z-Score, the Lumbar Body Mass Index (LBMD), the 10-year risk of femoral osteoporotic fracture (10-year fOHF risk) FRAX score, and the 10-year risk of major overall osteoporotic fracture (FRAX score) score.

Individuals who were eligible to participate in the study were separated into two groups: the first group, known as Cohort I, consisted of people whose vitamin D levels were lower than 30 ng/ml, and the second group, known as Cohort II, was comprised of people whose vitamin D levels were higher than 30 ng/ml. These two dichotomized cohorts were subjected to a Chi Square test in order to present the comparison results in terms of the number of percentages, the strength of associations (odd ratios), the Pearson chi-square statistic (χ 2), the Goodness of Fit (G-Test of independence), and the Pearson (r) and Spearman (ρ) correlations.

A Binary Logistic Regression Test was carried out in order to investigate the connection between the levels of Vitamin D in the patients and a number of different factors. These factors included a femoral hip bone mineral density (fH_BMD) of at least 0.755 g/cm2, a 10-year risk of femoral hip osteoporotic fractures based on the FRAX tool (fHOPF risk-free tool) of at least 3%, a lumbar bone mineral density (LBMD) of at least 0.835 g/cm2, and a 10-year risk of overall major osteoporotic fractures based on the FRAX tool (OPF_FRAX tool) of at least 20%.

We used logistic regression analyses in our research to investigate the extent of correlations, the range of total variations in the four investigated dependent variables (VR), the percentage of cases that can be explained by the vitamin D level, and the predictive accuracy of each tested dependent variable based on the vitamin D level. All of these factors were taken into consideration in order to determine the range of total variations. In order to derive the coefficients that are necessary to represent the corresponding Binary Logistic Regression models that were investigated, this test was carried out.

Through the utilisation of the Receiver Operating Characteristic (ROC) and sensitivity analysis, we carried out a comprehensive and methodical examination of the data that was supplied by the participants. This made it possible for us to investigate the area under the ROC curve (AUROC) and identify the cut-off points that were most effective. In addition, we computed a number of different sensitivity indices, including sensitivity, positive and negative predictive values, the Youden index, the accuracy index, and specificity.

Following the construction of the logistic regression models and the establishment of the serial vitamin D cutoff points, we graphically represented the correlation between the logistic regression and the probability of achieving the dichotomized level for each of the four dependent variables that were predefined. For the purpose of conducting the statistical analysis, the Statistical Package for Social Science (SPSS) software, version 23.0, was utilised. The level of statistical significance that was determined to be significant was set at 5%.

3. Results

In total, 206 cases were examined for this study. Out of these, 103 cases were identified as having a positive actual state, which was indicated by a femoral hip bone mineral density (fH_BMD) of 0.755 g/cm2 or higher. Similar to the previous example, 103 cases were identified as having a negative actual state, which was also indicated by a fH_BMD value of ≥0.755 g/cm2. In addition, five cases were not included in the analysis because there was evidence that was missing. Indicators of a more compelling evidence for a favourable current condition include elevated levels of vitamin D.

The study conducted an examination of the AUROC±SEM, which yielded a value of 0.981±0.009 (95% confidence interval; 0.964-0.998). With a sensitivity of 93.2%, a false positive rate of 5.8%, and a true positive rate of 99%, the optimal level of vitamin D for optimal operation was determined to be 27.25 ng/ml in this study. Youden's index was used to make this determination. An overall total of 206 cases were examined for this study. Following the application of the Fracture Risk Assessment Tool, a total of 96 cases were categorised as positive. This classification was based on a 10-year risk of femoral hip related osteoporotic fracture (10-year fH_OPF risk_FRAX) that was equal to or greater than 3%.

On the other hand, 110 cases were categorised as negative, with a 10-year fH_OPF risk_FRAX of less than three percent. Additionally, there were five cases that lacked data. The presence of a positive current condition is more strongly supported by lower levels of vitamin D expression. After conducting an analysis, the area under the receiver operating characteristic curve (AUROC) was determined to be 0.965±0.012, with a 95% confidence interval ranging from 0.942 to 0.988.

This value was obtained by adding or subtracting the standard error of the mean (SEM). We used Youden's index to determine that the optimal level of vitamin D for optimal operation is 27.25 ng/ml. This was determined through the course of this research. Both the sensitivity and the false positive rates were found to be 93.8% and 7.3%, respectively. In total, 206 cases were examined for this study. One hundred and fifty of these cases were deemed to be positive on the basis that their lumbar bone mineral density (LBMD) was greater than or equal to 0.835 g/cm2. 51 cases were deemed to be negative because their LBMD was greater than or equal to 0.755 g/cm2, which was the threshold for determination.

Additionally, there were five cases that lacked data. The presence of elevated levels of vitamin D is a more robust indication of a favourable current condition. After conducting an analysis, the area under the receiver operating characteristic curve (AUROC) was determined to be 0.739±0.034, with a 95% confidence interval ranging from 0.672 to 0.806. This value was obtained by adding or subtracting the standard error of the mean (SEM). We used Youden's index to determine that the optimal level of vitamin D for optimal operation is 27.05 ng/ml. This was determined through the course of this research. After conducting the analysis, it was discovered that the sensitivity rate was 57.94%, while the false positive rate was 9.8%. In total, 206 cases were examined for this study.

Out of these, 49 cases were found to have a positive actual state, which indicates a major osteoporotic fracture risk of at least 20% over a period of ten years, according to the Fracture Risk Assessment Tool (FRAX). There were 157 cases, on the other hand, that were categorised as having a negative actual state, and according to FRAX, the risk of major osteoporotic fractures occurring over a period of ten years was less than twenty percent. In addition, five of the cases were excluded from the analysis because lacking data was present in them. Indicators of a more compelling evidence for a favourable current condition include decreased levels of vitamin D.

Following an examination, the area under the receiver operating characteristic curve (AUROC) was determined to be 0.734±0.035, with a 95% confidence interval ranging from 0.666-0.802. This value was obtained by adding or subtracting the standard error of the mean (SEM). We used Youden's index to determine that the optimal level of vitamin D for optimal operation is 27.05 ng/ml. This was determined through the course of this research.

At this level, the sensitivity was found to be 89.8 percent, and the false positive rate was found to be 33.1 percent. The AUROC±SEM was highest for the fH_BMD≥0.755 g/cm2 dependent variable [0.981±0.009 (95% CI; 0.964-0.998)], followed by the 10-year fH_OPF risk_FRAX tool ≥3% [0.965±0.012 (95% CI; 0.942-0.988)], LBMD≥0.835 g/cm2 [0.739±0.034 (95% CI; 0.672-0.806)], and finally the 10-year overall major OPF_FRAX tool ≥20% [0.734±0.035 (95% CI; 0.666-0.802)].

In order to simulate the relationship between the levels of vitamin D in the patients who were tested and their femoral hip bone mineral density (fH_BMD), a Binary Logistic Regression model was developed. A representation of the model can be found in the equation [e (-22.27+0.829×Vitamin D level) /1+ e (-22.27+0.829×Vitamin D level)]. The probability that the patient's fH_BMD would be equal to or higher than 0.755 g/cm2 at the optimal level of Vitamin D, which was 27.25 ng/ml, was 61.39%.

A Binary Logistic Regression model was developed in order to simulate the association between the Vitamin D levels of patients who were tested and their 10-year risk of femoral hip osteoporotic fractures. This risk was determined by the FRAX tool (fH_OPF risk_FRAX tool) and was equal to or greater than 3%. The model equation is represented by the expression [e (12.057-0.478×Vitamin D level) /1+ e (12.057-0.478×Vitamin D level)]. As determined by the fH_OPF risk_FRAX tool, the probability of a patient's fracture risk being equal to or greater than 3% was 27.25% when the optimal explored Vitamin D level was 27.25 ng/ml. This was the case when the patient was at the optimal level.

4. Discussion

The effects of serum 25-OH-Cholecalciferol, which is a reliable marker for overall vitamin D levels, on microarchitectural bone health, specifically osteoporotic fractures, have been investigated in previous research. These studies include retrospective observational studies, prospective randomised clinical trials (RCTs), and meta-analyses. On the other hand, these studies have produced results that are contradictory, with a tendency to favour positive outcomes rather than neutral or negative outcomes. It is unfortunate that the majority of the randomised controlled trials (RCTs) that have been conducted in the past have frequently been limited by insufficient statistical power to detect differences. [16-17]

This is primarily due to the fact that the sample sizes were small and the patterns of vitamin D administration were inconsistent. As an illustration, a mendelian randomization trial discovered that the serum vitamin D levels that were

measured did not have any beneficial impact on osteoporotic fractures. It is possible that the negative effects of the mendelian RTC can be attributed to the fact that the study had a weak instrument bias and that it was evaluated in populations that had a low overall risk of fracture. Furthermore, the evaluation of numerous contradictory meta-analysis studies was made more difficult due to the significant variability in the criteria used for including or excluding data. [17-18]

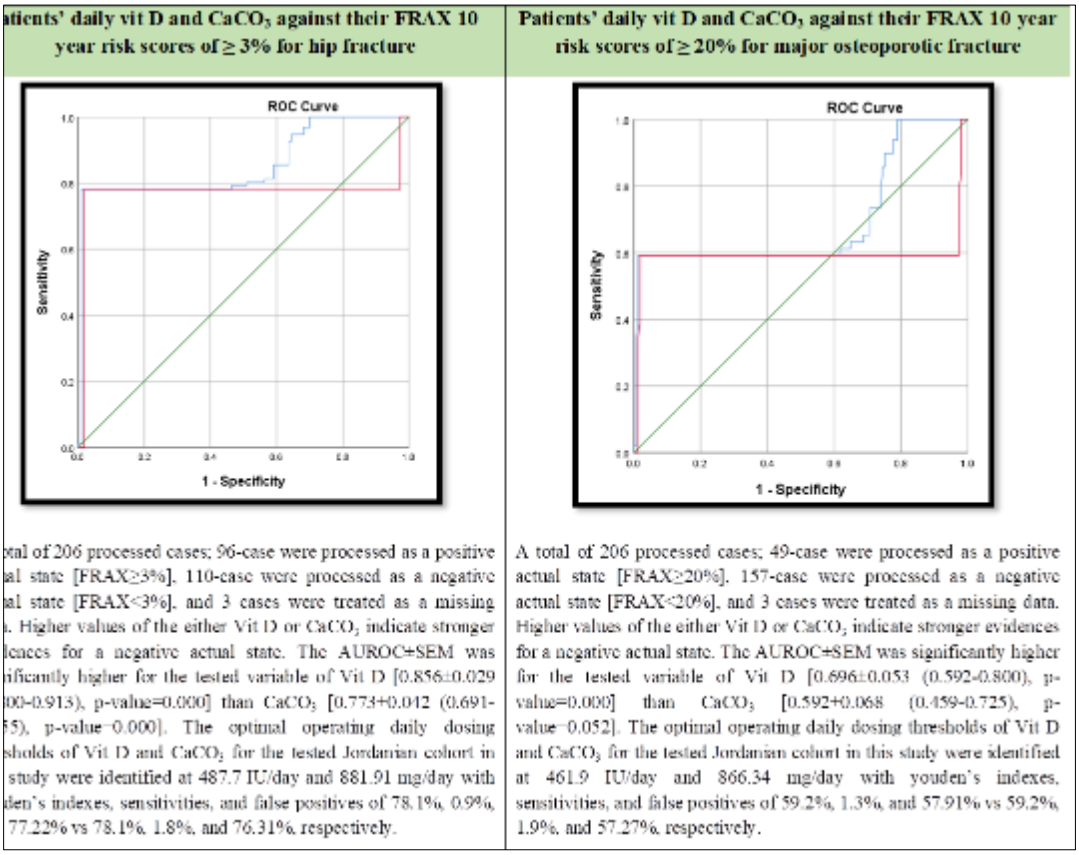


Figure 1 The Receiver Operating Characteristic (ROC) analysis were individually constructed to explore the area under the ROC curves (AUROCs) for the patients' daily vit D and $CaCO_3$ against their FRAX 10-year risk scores of ≥ 3% for hip fracture or ≥ 20% for major osteoporotic fracture, in studied patients who attended to our rehabilitation and rheumatology clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan. The AUROC±SEM was significantly higher for both the daily Vit D and $CaCO_3$ versus FRAX≥3% than versus FRAX≥20%

This made the evaluation of these studies increasingly difficult. Ginsberg et al. and Barbour et al. both conducted studies that demonstrated that there is no significant correlation between hip fractures and non-spine fractures in relation to vitamin D levels, respectively. These findings are similar to one another. There is a consistent positive relationship between vitamin D levels and various measures of bone quality, as demonstrated by the findings of our study as well as the findings of other studies. Both the research carried out by Looker et al. and the research carried out by Holvik et al. demonstrated that elderly patients who had lower levels of serum 25-OH-Cholecalciferol had a significantly increased risk of osteoporotic fractures. [19-20]

In terms of public health, osteoporosis and the fractures that are associated with it are a major concern on a global scale. The importance of us working together and taking into account all of the potential factors that can have a negative impact on bone quality cannot be overstated. This includes using comprehensive regression models to simulate the complex interactions between factors such as body measurements, nutrition, other health conditions, ageing, medication use, mineral and vitamin deficiencies or supplements, secondary metabolic disorders, geographical and racial differences, and physical activity levels. To lessen the likelihood of osteoporotic fractures, the most recent recommendations recommend that elderly men and women who have gone through menopause should take a daily dose of calcium and vitamin D that is equal to 1200 milligrammes and 800 international units, respectively. [21-24]

In this study, for the purpose of simulating the relationship between the levels of vitamin D in patients who were tested and their lumbar bone mineral density (LBMD) being greater than or equal to 0.835 g/cm2, a Binary Logistic Regression model was developed. [e (-1.455+0.109×Vitamin D level) /1+ e (-1.455+0.109×Vitamin D level)] is the equation that represents the model. If a patient had an optimal vitamin D level of 27.05 ng/ml, there was an 81.66% chance that they would have a Lumbar Bone Mineral Density (LBMD) value that was greater than or equal to 0.835 g/cm2.

Using the Fracture Risk Assessment Tool (FRAX) and a 10-year major osteoporotic fracture risk of 20% or higher, a Binary Logistic Regression model was developed in order to simulate the association between the Vitamin D levels of patients who were tested and their overall risk of major osteoporotic fractures over a period of ten years. The model equation is represented by the expression [e (1.306-0.105×Vitamin D level) /1+ e (1.306-0.105×Vitamin D level)]. At a vitamin D level of 27.05 ng/ml, the optimal level, it was discovered that the likelihood of a patient having a major osteoporotic fracture risk (FRAX) of 20% or higher over a period of ten years was 17.74%.

Table 1 The Binary Logistic Regression results for the patients' daily vit D and CaCO3 against their FRAX 10-year risk scores of ≥ 3% for hip fracture or ≥ 20% for major osteoporotic fracture, in studied patients who attended to our rehabilitation and rheumatology clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan

Tested variables	**B±SEM**	**Wald**	**Sig.**	**Exp(B)**	**95% C.I.for EXP(B)**		**χ2(df)**	**VR**	**%Cases**
					Lower	**Upper**			
FRAX≥3%	e (26.512-0.052×Vit D) /1+ e (26.512-0.052×Vit D)								
Vit D (IU/day)	-0.052±0.006	67.471	0.000	0.950	0.938	0.961	(8) 63.633	46.1%-61.6%	86.4%
Constant	26.512±3.282	65.245	0.000	3.27×1011					
FRAX≥3%	e (11.092-0.012×CaCO3) /1+ e (11.092-0.012×CaCO3)								
CaCO3 (mg/day)	-0.012±0.003	21.278	0.000	0.988	0.983	0.993	(8) 177.960	11.5%-15.3%	79.6%
Constant	11.092±2.430	20.834	0.000	6.56×104					
FRAX≥20%	e (6.831-0.016×Vit D) /1+ e (6.831-0.016×Vit D)								
Vit D (IU/day)	-0.016±0.004	14.007	0.000	0.984	0.976	0.993	(8) 89.121	7%-10.6%	76.2%
Constant	6.831±2.115	10.432	0.001	926.537					
FRAX≥20%	e (-2.592+0.002×CaCO3) /1+ e (-2.592+0.002×CaCO3)								
CaCO3 (mg/day)	0.002±0.003	0.360	0.548	1.002	0.997	1.007	(8) 131.811	2%-3%	76.2%
Constant	-2.592±2.389	1.177	0.278	0.075					

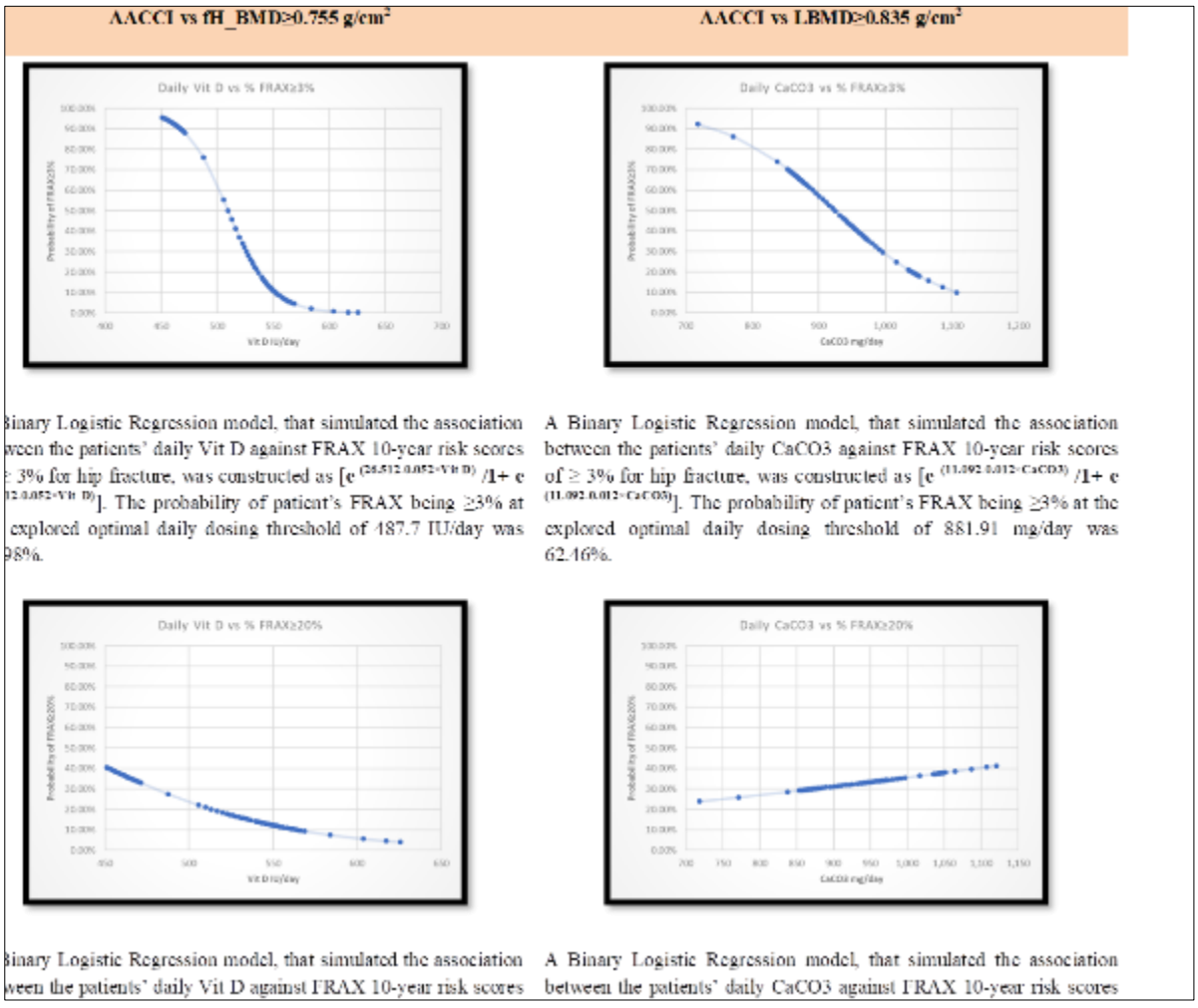
The Binary Logistic Regression Test was conducted for the patients' daily vit D and CaCO3 against the patients' FRAX 10-year risk scores of ≥ 3% for hip fracture or ≥ 20% for major osteoporotic fracture [either probability of ≥3 or ≥20% (signed as 1 and considered as a positive actual state) or probability of ≤ 3% or ≤20% (signed as 0 and considered as a negative actual state)], to explore the degree of correlations, how range of the total variations in the dependent variable (VR) and % of cases that can be explained by the independent variable, and the quality of the prediction of the dependent variable. Also, this test was conducted to abstract the necessary coefficients to present the explored Binary Logistic Regression models.

The percentage of the dependent variable that can be accounted for by our model ranges from thirty percent to forty two percent, depending on whether the Cox & Snell R2 method or the Nagelkerke R2 method is utilised. In addition, our model correctly classified 78.2 percent of the cases under consideration. In the course of our research, we discovered that the optimal combination of Vitamin D and calcium carbonate to reduce the risk of hip osteoporotic fracture (FRAX<3%) and overall major risk over a 10-year period (FRAX<20%) in our Jordanian cohort was a minimum of 487.7 International Units (IU) with 881.91 mg/day and 461.9 IU with 866.34 mg/day, respectively. In particular with regard to the Middle East region, this finding is exclusive to our research process.

Table 2 The optimal cut-off points, sensitivities, specificities, positive and negative predictive values and likelihoods ratios, and Youden and accuracy indices of the patients' daily vit D and $CaCO_3$ against their FRAX 10-year risk scores of ≥ 3% for hip fracture or ≥ 20% for major osteoporotic fracture, in studied patients who attended to our rehabilitation and rheumatology clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan

OI	Cutoff	TPR	FPR	YI	TNR	PPV	NPV	NLR	PLR	AI
FRAX≥3%										
Vit D (IU/day)	487.7	78.1%	0.9%	77.22%	99.09%	98.68%	83.85%	22.08%	8593.75%	89.32%
$CaCO_3$ (mg/day)	881.91	78.1%	1.8%	76.31%	98.18%	97.40%	83.72%	22.28%	4296.88%	88.83%
FRAX≥20%										
Vit D (IU/day)	461.9	59.2%	1.3%	57.91%	98.73%	93.55%	88.57%	41.34%	4645.92%	89.32%
$CaCO_3$ (mg/day)	866.34	59.2%	1.9%	57.27%	98.09%	90.63%	88.51%	41.61%	3097.28%	88.83%

OI: Outcomes of interest, TPR: True positive rate (sensitivity), FPR: False positive rate, YI: Youden index, TNR: True negative ratio (specificity), PPV: Positive predictive value, NPV: Negative predictive value, AI: Accuracy index, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio.



inary Logistic Regression model, that simulated the association ween the patients' daily Vit D against FRAX 10-year risk scores 3% for hip fracture, was constructed as [e $^{(26.512\ 0.052\times Vit\ D)}$ /1+ e $^{(26.512\ 0.052\times Vit\ D)}$]. The probability of patient's FRAX being ≥3% at explored optimal daily dosing threshold of 487.7 IU/day was 98%.

A Binary Logistic Regression model, that simulated the association between the patients' daily CaCO3 against FRAX 10-year risk scores of ≥ 3% for hip fracture, was constructed as [e $^{(11.092\ 0.012\times CaCO3)}$ /1+ e $^{(11.092\ 0.012\times CaCO3)}$]. The probability of patient's FRAX being ≥3% at the explored optimal daily dosing threshold of 881.91 mg/day was 62.46%.

inary Logistic Regression model, that simulated the association ween the patients' daily Vit D against FRAX 10-year risk scores

A Binary Logistic Regression model, that simulated the association between the patients' daily CaCO3 against FRAX 10-year risk scores

Figure 2 The Binary Logistic Regression model's illustrations for the patients' daily vit D and CaCO3 against their FRAX 10-year risk scores of ≥ 3% for hip fracture or ≥ 20% for major osteoporotic fracture, in studied patients who attended to our rehabilitation and rheumatology clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan

Table 3 Comparatively studied variables for the studied patients across Cohort I-II; Lower Vit D levels cohort (Cohort I) versus Higher Vit D levels cohort (Cohort II), between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan

	Cohort I Lower Vit D cohort (Vit D<30 ng/ml) (143, 69.42%)	**Cohort II Higher Vit D cohort (Vit D≥30 ng/ml) (63, 30.58%)**	**Total (206, 100%)**	**OR**	**R ρ**	**χ^2 G-Test**	**p-Value**
Gender							
Female	122 (85.3%)	54 (85.7%)	176 (85.4%)	0.968 (95% CI; 0.416-2.252)	-0.005±0.069 -0.005±0.069	0.006 0.006	0.940
Male	21 (14.7%)	9 (14.3%)	30 (14.6%)				
Female: Male	5.81: 1	6: 1	5.87: 1				
Age (Yrs)							
50-59	49 (34.3%)	61 (96.8%)	110 (53.4%)	0.017 (95% CI; 0.004-0.073)	- 0.578±0.044* - 0.578±0.044*	68.781 83.053	0.000
60-69	94 (65.7%)	2 (3.2%)	96 (46.6%)				
BMI (Kg/m^2)							
18.5-24.9	15 (10.5%)	1 (1.6%)	16 (7.8%)	NA	0.343±0.043* 0.374±0.040*	31.545 43.148	0.000
25-29.9	35 (24.5%)	0 (0.0%)	35 (17.0%)				
30-34.9	93 (65.0%)	59 (93.7%)	152(73.8%)				
>=35	0 (0.0%)	3 (4.8%)	3 (1.5%)				
WrC (cm)							
16-18 (M)	77 (53.8%)	8 (12.7%)	85 (41.3%)	8.021 (95% CI; 3.564-18.053)	0.385±0.056* 0.385±0.056*	30.551 33.903	0.000
19-21 (L)	66 (46.2%)	55 (87.3%)	121 (58.7%)				
PD (g/100 Cal)							
Lower<2.5	75 (52.4%)	2 (3.2%)	77 (37.4%)	33.640 (95% CI; 7.921-142.862)	0.469±0.043* 0.469±0.043*	45.361 56.674	0.000
Higher≥2.5	68 (47.6%)	61 (96.8%)	129(62.6%)				
FVC							
Intermittent	19 (13.3%)	2 (3.2%)	21 (10.2%)	4.673 (95% CI; 1.054-20.714)	0.154±0.049* 0.154±0.049*	4.885 5.893	0.000
Regular	124 (86.7%)	61 (96.8%)	185 (89.8%)				
Menopausal age (Yrs)							
40-44.9	14 (11.7%)	1 (1.9%)	15 (8.7%)	NA	0.046±0.069 0.044±00.072	5.342 6.533	0.148
45-49.9	51 (42.5%)	26 (50.0%)	77 (44.8%)				
50-54.9	41 (34.2%)	21 (40.4%)	62 (36.0%)				
≥55	14 (11.7%)	4 (7.7%)	18 (10.5%)				
AACCI							
<5	89 (62.2%)	55 (87.3%)	144(69.9%)	0.240 (95% CI; 0.106-0.542)	- 0.252±0.057* - 0.252±0.057*	13.058 14.471	0.000
≥5	54 (37.8%)	8 (12.7%)	62 (30.1%)				

Table 4 (Continued). Comparatively studied variables for the studied patients across Cohort I-II; Lower Vit D levels cohort (Cohort I) versus Higher Vit D levels cohort (Cohort II), between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan

	Cohort Lower Vit D cohort (Vit D<30 ng/ml) (143, 69.42%)	**Cohort II Higher Vit D cohort (Vit D≥30 ng/ml) (63, 30.58%)**	**Total (206, 100%)**	**OR**	**R ρ**	**χ 2 G-Test**	**p-Value**
FRAX score							
<3%	49 (34.3%)	61(96.8%)	110(53.4%)	0.017 (95% CI; 0.004-0.073)	-0.578±0.044* -0.578±0.044*	68.781 83.053	0.000
≥3%	94 (65.7%)	2 (3.2%)	96 (46.6%)				
fH_BMD (g/cm2)							
<0.755	101 (70.6%)	2 (3.2%)	103 (50%)	73.345 (95% CI; 17.141--313.834)	0.622±0.044* 0.622±0.044*	79.597 94.686	0.000
≥0.755	42 (29.4%)	61 (96.8%)	103 (50%)				
FRAX score							
<20%	96 (67.1%)	61 (96.8%)	157 (76.2%)	0.067 (95% CI; 0.016-0.286)	-0.321±0.043* -0.321±0.043*	21.269 27.185	0.000
≥20%	47 (32.9%)	2 (3.2%)	49 (23.8%)				
LBMD (g/cm2)							
<0.835	49 (34.3%)	2 (3.2%)	51 (24.8%)	15.899 (95% CI; 3.729-67.79)	0.332±0.043* 0.332±0.043*	22.694 29.005	0.000
≥0.835	94 (65.7%)	61 (96.8%)	155 (75.2%)				
Vit D level (ng/ml)							
10-19.9	66 (46.2%)	0 (0.0%)	66 (32.0%)	NA	0.831±0.015* 0.843±0.022*	206.000 253.676	0.000
20-29.9	77 (53.8%)	0 (0.0%)	77 (37.4%)				
30-39.9	0 (0.0%)	55 (87.3%)	55 (26.7%)				
40-49.9	0 (0.0%)	6 (9.5%)	6 (2.9%)				
50-59.9	0 (0.0%)	1 (1.6%)	1 (0.5%)				
≥60	0 (0.0%)	1 (1.6%)	1 (0.5%)				

Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi Square Test (at p-value< 0.05) and expressed as Number (Percentage). The strength of associations was also described as odd ratios (OR). The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The Goodness of Fit (G-Test of independence) which uses the log of the ratio of two likelihoods and tests the goodness of fit of observed frequencies to their expected. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value. The studied patients were dichotomously categorized into 2 comparative cohorts; cohort whose Vit D levels was <30 ng/ml [Cohort I] versus cohort whose Vit D level was ≥30 ng/ml [Cohort II].; FRAX: Fracture risk assessment tool; LBMD: Lumbar bone mineral density; BMD: Bone mineral density in g per cm2; fH_BMD: Femoral hip bone mineral density.

Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi Square Test (at p-value< 0.05) and expressed as Number (Percentage). The strength of associations was also described as odd ratios (OR). The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The Goodness of Fit (G-Test of independence) which uses the log of the ratio of two likelihoods and tests

the goodness of fit of observed frequencies to their expected. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value. The studied patients were dichotomously categorized into 2 comparative cohorts; cohort whose Vit D levels was <30 ng/ml [Cohort I] versus cohort whose Vit D level was ≥30 ng/ml [Cohort II]; ACCI: Age adjusted Charlson Comorbidity Index; BMI: Body mass index; PD: Protein density; WrC: Wrist circumference in cm.; FVC: Fruit and vegetable content.

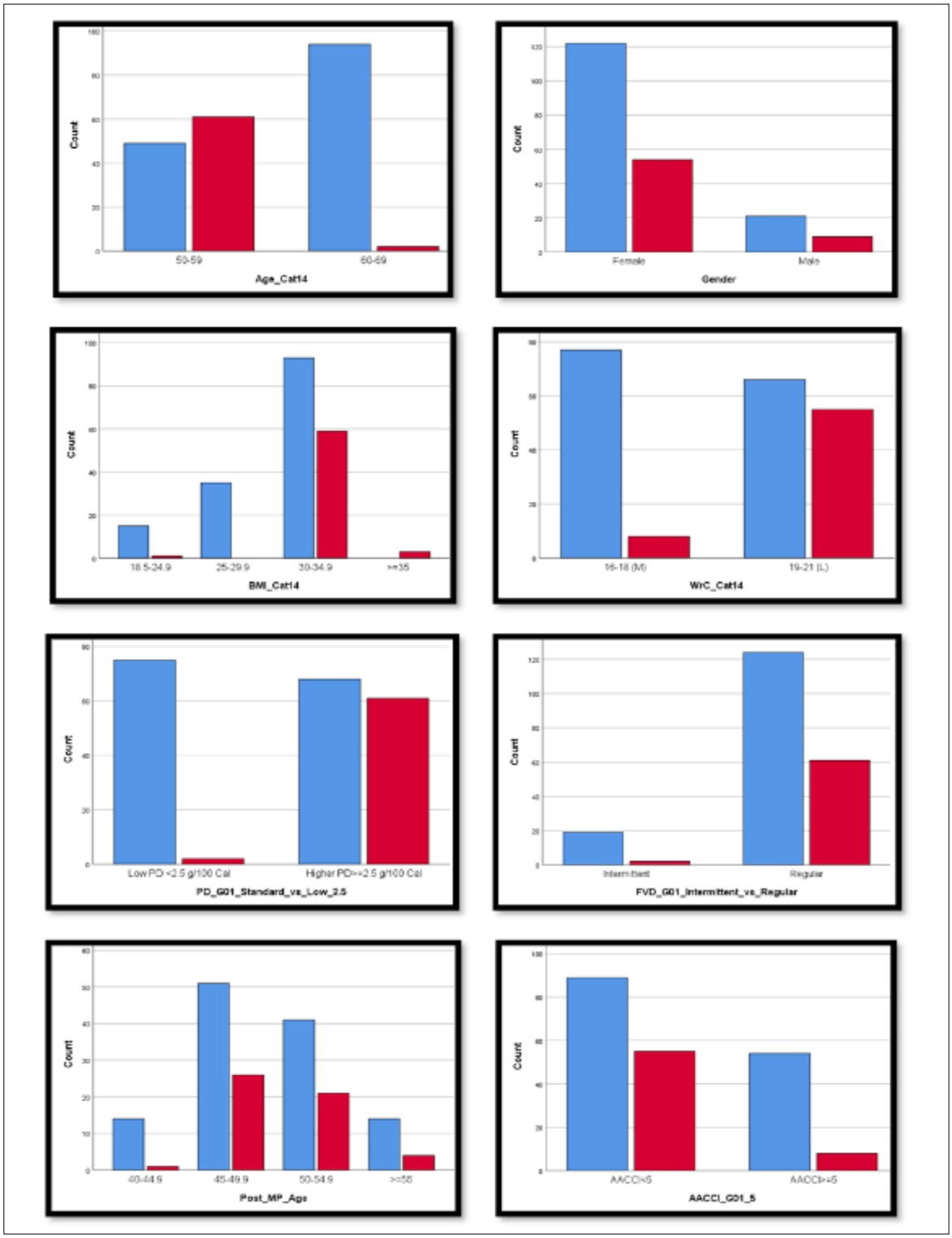


Figure 3 Bar charts' visualizations for the studied patients across Cohort I-II; Lower Vit D levels cohort (Cohort I) versus Higher Vit D levels cohort (Cohort II), between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan

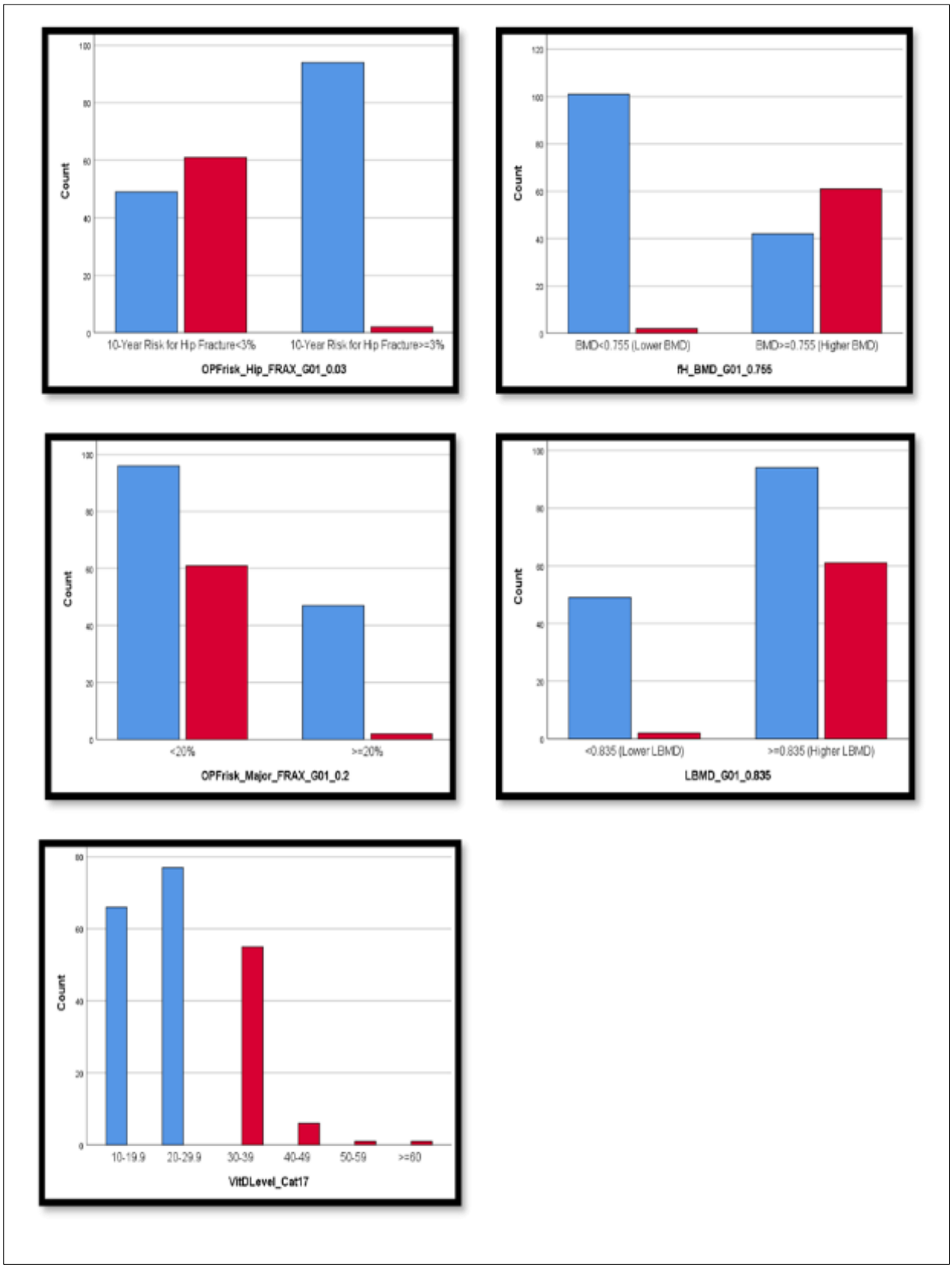


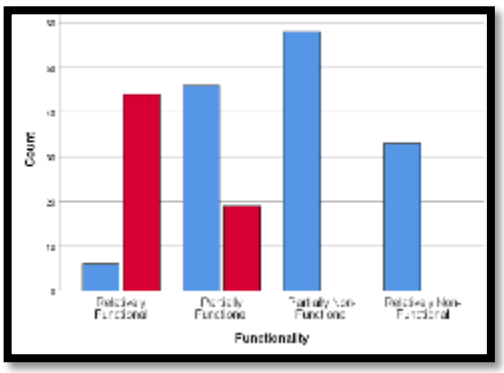
Figure 4 (Continued). Bar charts' visualizations for the studied patients across Cohort I-II; Lower Vit D levels cohort (Cohort I) versus Higher Vit D levels cohort (Cohort II), between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan.

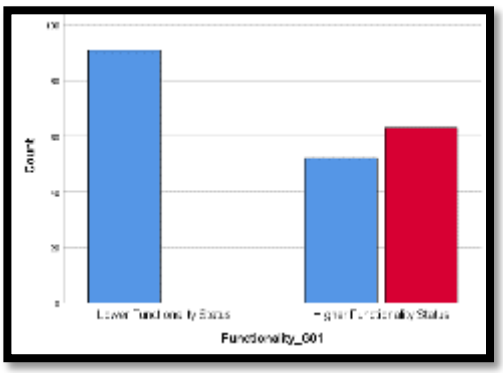
Table 5 (Continued). Comparatively studied variables for the studied patients across Cohort I-II; Lower Vit D levels cohort (Cohort I) versus Higher Vit D levels cohort (Cohort II), between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan.

	Cohort I Lower Vit D cohort (Vit D<30 ng/ml) (143, 69.42%)	**Cohort II Higher Vit D cohort (Vit D≥30 ng/ml) (63, 30.58%)**	**Total (206, 100%)**	**OR**	**R ρ**	**χ^2 G-Test**	**p-Value**
Functionality							
Relatively Functional	6 (4.2%)	44 (69.8%)	50(24.3%)	NA	-0.690±0.032* -0.703±0.033*	117.792 138.437	0.000
Partially Functional	46 (32.2%)	19 (30.2%)	65(31.6%)				
Partially Non-Functional	58 (40.6%)	0 (0.0%)	58(28.2%)				
Relatively Non-Functional	33 (23.1%)	0 (0.0%)	33(16.0%)				
Functionality							
Lower	91 (63.6%)	0 (0.0%)	91 (44.2%)	2.212 (95% CI; 1.809-2.704)	0.590±0.039* 0.590±0.039*	71.815 95.306	0.000
Higher	52 (36.4%)	63 (100.0%)	115(55.8%)				
Alendronate							
No	49 (34.3%)	61 (96.8%)	110 (53.4%)	0.017 (95% CI; 0.004-0.073)	-0.578±0.044* -0.578±0.044*	68.781 83.053	0.000
Yes	94 (65.7%)	2 (3.2%)	96 (46.6%)				
Smoking							
No	105 (73.4%)	57 (90.5%)	162 (78.6%)	0.291 (95% CI; 0.116-0.729)	-0.192±0.057* -0.192±0.057*	7.568 8.484	0.006
Yes	38 (26.6%)	6 (9.5%)	44 (21.4%)				
Cs							
No	118 (82.5%)	58 (92.1%)	176 (85.4%)	0.407 (95% CI; 0.148-1.118)	-0.125±0.059 -0.125±0.059	3.203 3.525	0.074
Yes	25 (17.5%)	5 (7.9%)	30 (14.6%)				
fHx of fracture							
No	121 (84.6%)	60 (95.2%)	181 (87.9%)	0.275 (95% CI; 0.079-0.955)	-0.150±0.053* -0.150±0.053*	4.628 5.377	0.031
Yes	22 (15.4%)	3 (4.8%)	25 (12.1%)				

HTN							
No	45 (31.5%)	56 (88.9%)	101 (49.0%)	0.057 (95% CI; 0.024-0.136)	-0.529±0.054*	57.699	0.000
Yes	98 (68.5%)	7 (11.1%)	105 (51.0%)		-0.529±0.054*	63.426	
Anti-HTN							
CCBs	33 (33.7%)	0 (0.0%)	33 (31.4%)	NA	0.493±0.080*	54.018	0.000
CCBs+BBs	27 (27.6%)	0 (0.0%)	27 (25.7%)				
CCBs+ACEIs or ARBs	14 (14.3%)	0 (0.0%)	14 (13.3%)				
CCBs+Thiazide	19 (19.4%)	1 (14.3%)	20 (19.0%)		0.413±0.072*	31.129	
BBs+ACEIs or ARBs	5 (5.1%)	4 (57.1%)	9 (8.6%)				
ACEIs or ARBs+Thiazide	0 (0.0%)	2 (28.6%)	2 (1.9%)				
HT							
No	102 (71.3%)	56 (88.9%)	158 (76.7%)	0.311 (95% CI; 0.131-0.739)	-0.191±0.058*	7.546	0.006
Yes	41 (28.7%)	7 (11.1%)	48 (23.3%)		-0.191±0.058*	8.351	

Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi Square Test (at p-value< 0.05) and expressed as Number (Percentage). The strength of associations was also described as odd ratios (OR). The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The Goodness of Fit (G-Test of independence) which uses the log of the ratio of two likelihoods and tests the goodness of fit of observed frequencies to their expected. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value. The studied patients were dichotomously categorized into 2 comparative cohorts; cohort whose Vit D levels was <30 ng/ml [Cohort I] versus cohort whose Vit D level was ≥30 ng/ml [Cohort II].; Cs: Corticosteroids.; HTN: Hypertension.; Anti-HTN: anti hypertension.; fHx: Family history.; HT: Hypothyroidism.; CCBs: Calcium channel blockers.; BBs: Beta-blockers.; ACEIs: Angiotensin converting enzyme inhibitors.; ARBs: Angiotensin receptor blockers.





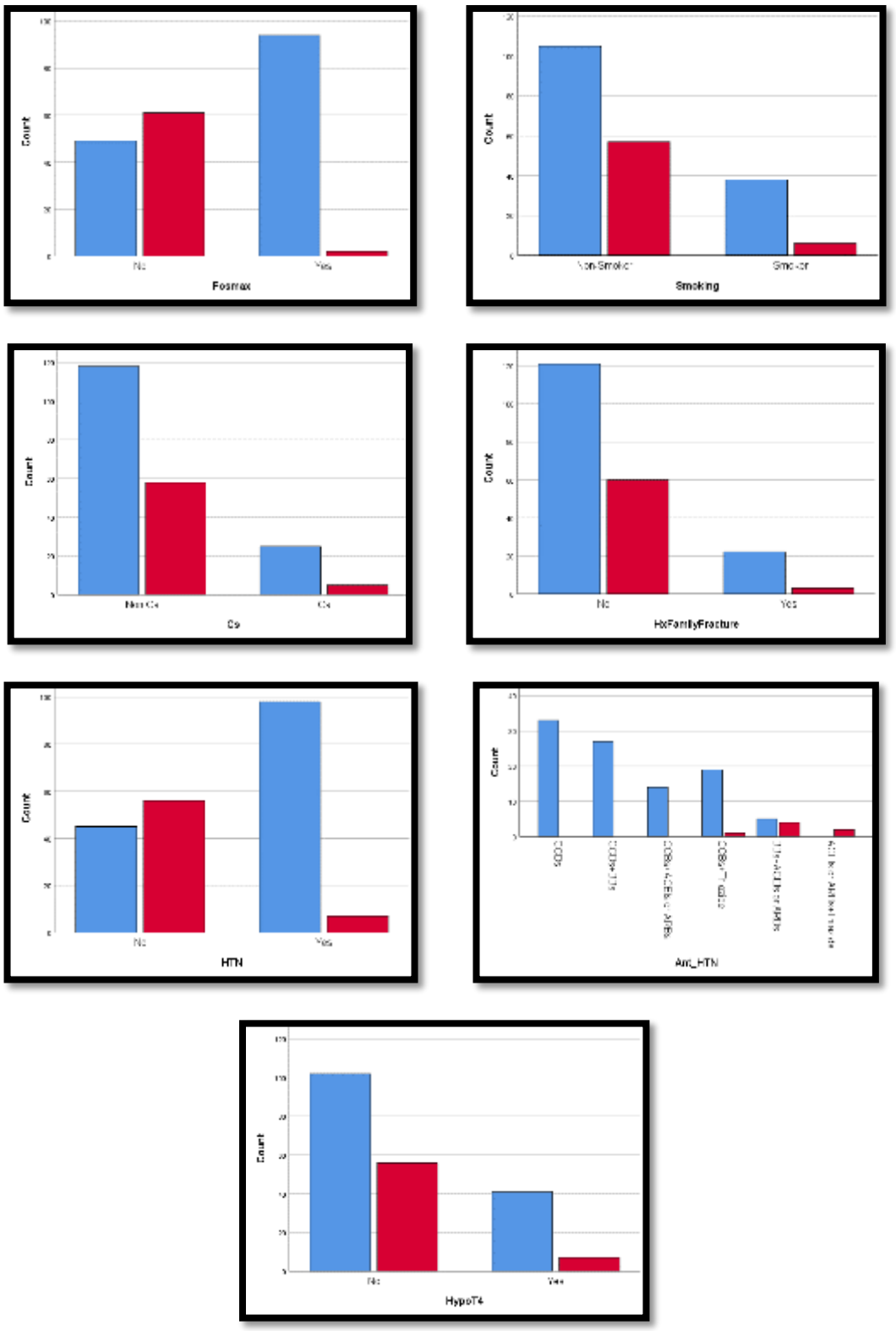


Figure 5 (Continued). Bar charts' visualizations for the studied patients across Cohort I-II; Lower Vit D levels cohort (Cohort I) versus Higher Vit D levels cohort (Cohort II), between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan

5. Conclusion

The results of our research showed that there is a direct connection between increased levels of vitamin D and improved bone mineral quality across a variety of indices that were investigated. There is a high probability that the serum 25-OH Cholecalciferol levels will demonstrate a protective effect on the bone health status. The retrospective nature of this study, the fact that it was carried out at a single location, and the relatively small sample size are all factors that contribute to the limitations of this research. It is necessary to conduct a comprehensive study that involves multiple sites and takes into consideration a variety of factors that may influence the results in order to accurately determine the causal relationship that exists between the levels of vitamin D and the various bone quality indices.

Compliance with ethical standards

Acknowledgments

Our appreciation goes to staff of the departments of Royal Medical Services for their enormous assistance and advice.

Disclosure of conflict of interest

There is no conflict of interest in this manuscript

Statement of ethical approval

There is no animal/human subject involvement in this manuscript

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

References

[1] Watts NB, Manson JE. Osteoporosis and fracture risk evaluation and management: shared decision making in clinical practice.JAMA. 2017;317(3):253-254.

[2] Wang Y, Tao Y, Hyman ME, Li J, Chen Y. Osteoporosis in China. Osteoporos Int. 2009;20(10):1651-1662.

[3] Lund CA, Møller AM, Wetterslev J, Lundstrøm LH. Organizational factors and long-term mortality after hip fracture surgery: a cohort study of 6143 consecutive patients undergoing hip fracture surgery. PLoS One. 2014;9.

[4] Li G, Thabane L, Papaioannou A, Ioannidis G, Levine MA, Adachi JD. An overview of osteoporosis and frailty in the elderly. BMC Musculoskelet Disord. 2017;18(1):46.

[5] Beaupre LA, Jones CA, Saunders LD, Johnston DW, Buckingham J, Majumdar SR. Best practices for elderly hip fracture patients. A systematic overview of the evidence. J Gen Intern Med. 2005;20(11):1019–25.

[6] Curtis EM, van der Velde R, Moon RJ, et al. Epidemiology of fractures in the United Kingdom, 1988-2012: variation with age, sex, geography, ethnicity and socioeconomic status. Bone. 2016;87:19-26.

[7] Tanner SB, Harwell SA. More than healthy bones: a review of vitamin D in muscle health. Ther Adv Musculoskelet Dis. 2015;7:152–9.

[8] van Schoor NM, Visser M, Pluijm SM, Kuchuk N, Smit JH, Lips P. Vitamin D deficiency as a risk factor for osteoporotic fractures. Bone. 2008;42:260–6.

[9] Yao P, Sun L, Lu L, et al. Effects of genetic and nongenetic factors on total and bioavailable 25(OH)D responses to vitamin D supplementation.J Clin Endocrinol Metab. 2017;102(1):100-110.

[10] Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know.J Clin Endocrinol Metab. 2011;96(1):53-58.

[11] Yao P, Lu L, Hu Y, et al. A dose-response study of vitamin D3 supplementation in healthy Chinese: a 5-arm randomized, placebo-controlled trial. Eur J Nutr. 2016;55(1):383-392.

[12] Fu Y, Hu Y, Qin Z, Zhao Y, Yang Z, Li Y, Liang G. Lv tion of serum 25- hydroxyvitamin D status with bone mineral density in 0-7 year old children. Oncotarget. 2016;7:80811–9.

[13] Bleicher K, Cumming RG, Naganathan V, Blyth FM, Le Couteur DG, Handelsman DJ, Waite LM, Seibel MJ. U-shaped association between serum 25-hydroxyvitamin D and fracture risk in older men: results from the prospective population-based CHAMP study. J Bone Miner Res. 2014;29: 2024–31.

[14] Zhang L, Chun C, Yang Y, et al. Vitamin D deficiency/insufficiency is associated with risk of osteoporotic thoracolumbar junction vertebral fractures. Med Sci Monit. 2019;25:8260–8.

[15] Tanaka S, Kuroda T, Yamazaki Y, Shiraki Y, Yoshimura N, Shiraki M. Serum 25- hydroxyvitamin D below 25 ng/mL is a risk factor for long bone fracture comparable to bone mineral density in Japanese postmenopausal women. J Bone Miner Metab. 2014;32:514–23.

[16] Looker AC, Mussolino ME. Serum 25-hydroxyvitamin D and hip fracture risk in older U.S. white adults. J Bone Miner Res. 2008;23:143–50.

[17] Holvik K, Ahmed LA, Forsmo S, Gjesdal CG, Grimnes G, Samuelsen SO, Schei B, Blomhoff R, Tell GS, Meyer HE. Low serum levels of 25-hydroxyvitamin D predict hip fracture in the elderly: a NOREPOS study. J Clin Endocrinol Metab. 2013;98:3341–50.

[18] Ginsberg C, Katz R, de Boer IH, et al. The 24,25 to 25-hydroxyvitamin D ratio and fracture risk in older adults: the cardiovascular health study. Bone. 2018; 107:124–30.

[19] Barbour KE, Houston DK, Cummings SR, et al. Calciotropic hormones and the risk of hip and nonspine fractures in older adults: the health ABC study. J Bone Miner Res. 2012; 27:1177–85.

[20] Feng Y, Cheng G, Wang H, Chen B. The associations between serum 25- hydroxyvitamin D level and the risk of total fracture and hip fracture. Osteoporos Int. 2017;28(5):1641–52.

[21] Trajanoska K, Morris JA, Oei L, et al; GEFOS/GENOMOS Consortium and the 23andMe Research Team. Assessment of the genetic and clinical determinants of fracture risk: genome wide association and mendelian randomisation study. BMJ. 2018;362:k3225.

[22] Holick MF, Binkley NC, Bischoff-Ferrari HA, et al; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline.J Clin Endocrinol Metab. 2011;96(7): 1911-1930.

[23] Grossman DC, Curry SJ, Owens DK, et al; US Preventive Services Task Force. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US Preventive Services Task Force recommendation statement.JAMA. 2018;319(15):1592-1599.

[24] Riggs BL, Khosla S, Melton LJ 3rd. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res. 1998;13(5):763–73