Original Article

The correlation between vitamin B12 and folate levels and bone mineral density among the Saudi population in a primary care setting

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Abstract

Purpose: Bone health and osteoporosis are significant health problems in Saudi Arabia. Approximately 40%–50% of women and 25%–33% of men sustain osteoporotic fractures in their lifetimes. Hence, identifying the risk factors for osteoporosis is crucial in reducing the incidence of fractures. **Materials and Methods:** We retrospectively reviewed the electronic medical records of 557 patients (female 60%, male 40%) aged ≥18 years (mean age, 66.53 years [standard deviation ± 14.169]) who underwent bone mineral density (BMD) scans at the Department of Family Medicine & Polyclinics, King Faisal Specialist Hospital and Research Centre (KFSH&RC) between January 2004 and June 2019. Data collected included demographics, BMD values, vitamin B12 levels, and folate levels. **Results:** This study indicated that the prevalence rates of vitamin B12 and folate deficiencies among the study population were 8.4% and 1.3%, respectively. There was a statistically significant association between vitamin B12 levels and fracture risk (P =0.044). However, no statistically significant correlation was observed between BMD at either site (lumbar spine or femoral neck) and vitamin B12 (P =0.926.,070) and folate levels (P =.683.,79). BMD showed a significant positive correlation with body mass index at the lumbar spine and femoral neck (P = 0.000). There was no statistically significant association between vitamin B12 levels and the use of metformin (P =.26). **Conclusion:** Vitamin B12 is associated with fracture risk; however, vitamin B12 and folate levels are not correlated to BMD (femoral neck and lumbar spine).

Keywords: Bone health, B12 supplementation, folate supplementation, fracture risk, osteoporosis.

Introduction

Osteoporosis and bone health remain a major health problem often associated with significant morbidity, mortality, and healthcare costs.[1] An epidemiological analysis reported that 34% of healthy Saudi women and 30.7% of healthy Saudi men aged between 50 and 79 years are osteoporotic.[2] Furthermore, {Alwahhabi, 2015 #1}approximately 40%–50% of women and 25%–33% of men sustain osteoporotic fractures in their lifetimes. Hence, identifying the risk factors for osteoporosis is crucial in reducing the incidence of fractures. Several factors impact the development of osteoporosis; these are genetic factors; sex hormones, mainly estrogen; lifestyle features, such as smoking and alcohol consumption; hyperparathyroidism; hyperthyroidism; and nutritional deficiencies, such as deficiencies in vitamins and calcium.[3] Although vitamin D has received the most attention concerning Bone Mineral Density (BMD), recent studies have suggested that several other nutrients play an essential role in bone health.[4]

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Vitamin B12 is essential for DNA synthesis. Clinical and cell culture studies have indicated that low concentrations of vitamin B12 and folate demonstrate strong stimulatory effects on osteoclast activity and bone resorption, whereas elevated concentrations promote bone formation through their effects on osteoblast activity.[3-5]

Previous studies have investigated the association between serum vitamin B12 and folate levels and BMD and the findings have indicated significant differences as some studies found significant associations and others did not.[6-11] However, only one study investigated the relationship between vitamin B12 and folate levels and BMD in our local population in Saudi Arabia and only male patients were included in this research.[3] Hence, large, well-constructed future studies concerning this issue are warranted. Our study was more community-based than the previous study in Saudi Arabia, in that it was carried out at the primary care level. We think this study will contribute to the current understanding of the association between vitamin B12 and folate levels and osteoporosis in our local population.

Material and Methods

Design and setting

This is a retrospective study conducted at the Department of Family Medicine & Polyclinics, King Faisal Specialist Hospital and Research Centre (KFSH&RC);electronic medical records were reviewed from the Integrated Clinical Information System database between January 2004 and June 2019.

Study population and methodology

The electronic health records of 557 patients who had undergone BMD scanning and aged ≥18 years were collected (female 60% and male 40%). Participants with a history of vitamin B12 supplementation, folate supplementation, or osteoporosis medication before BMD were excluded. Demographic data, laboratory results, and radiology reports, including vitamin B12 levels, folate levels, and BMD values, were collected. The result closest to the radiology report was considered if there were multiple readings of vitamin B12 or folate levels.

A statistical data analysis was performed using SPSS software, version 25.0. Descriptive statistics for the continuous variables were reported as median and mean, and categorical variables were summarized as frequencies and percentages. Categorical variables were compared using the Chi-squared test. A *P* value <.05 was considered statistically significant. Pearson correlation was used to test the correlation between vitamin B12 and folate levels and BMD.

Ethical consideration

Although the information collected was anonymous, neither the patients' names nor the medical record numbers were used in the datasheet. Instead, unique patient number codes were used to ensure confidentiality and privacy. The study was approved by the ethical committee and institutional review board and complies with the policies of the Research Advisory Committee at KFSH&RC and the laws of the Kingdom of Saudi Arabia (RAC# 2181-061).

Results

The mean age of the recruited patients was 66.53 ± 14.169. Table 1 gives an overview of the study population.

BMD

Based on the BMD values at the lumbar spine and femoral neck, the patients were classified into the three following groups: (a) the normal group (T-score ≤ -1), n = 355 for the lumbar spine and n = 317 for the femoral neck; (b) the osteopenic group (-2.5 < T-score > -1), n = 159 for the lumbar spine and n = 202 for the femoral neck; and (c) the osteoporotic group (T-score ≥ -2.5), n = 43 for the lumbar spine and n = 38 for the femoral neck. Of 557 patients, 11% were found to have osteoporosis, 42% had osteopenia, and 47% had normal BMD.

Vitamin B12 and folate levels

The mean level for serum B12 was 344.32 (standard deviation ± 228.788); 8.4% of the population was found to have low B12 levels (< 145), 83.3% had normal B12 levels (145–637), and 8.3% had high levels of B12 (> 637; Figure 1). The mean

Table 1: Overview of study population

Total number of participants=557

Parameters	*n*	Percentage
Gender		
Male	223	40.0%
Female	334	60.0%
Smoking status		
Current smoker	32	5.8%
Ex-smoker	8	7.2%
Nonsmoker	330	59.8%
Not documented	182	33.0%
BMI		
Underweight	15	2.8%
Normal	98	18.5%
Overweight	166	31.3%
Obese	251	47.4%
History of fracture		
Yes	29	5.2%
No	527	94.8%
Vitamin B12 level		
Low	47	8.4%
Normal	464	83.3%
High	46	8.3%
Folate level		
Low	3	1.3%
Normal	81	35.4%
High	145	63.3%
BMD		
Normal	262	47.0%
Osteopenia	234	42.0%
Osteoporosis	61	11%

BMD, bone mineral density; BMI, body mass index

level for folate in our population was 2,202.10 (standard deviation ± 962.945). Among the patients, 1.3% were found to have low folate levels (< 776), 35.4% had normal folate levels (776–1,784), and 63.3% had high folate levels (> 1,784; Figure 2).

Correlation of BMD to vitamin B12 and folate levels

Correlation analysis of the features measured on the continuous scale was evaluated using Pearson's correlation and is displayed in a "heat map" [Figure 3]. The significance of these correlations is summarized in Table 2. Among the whole population, there was no statistically significant correlation between BMD at both sites (lumbar spine and femoral neck) and B12 or folate levels [Table 2].

History of fracture and vitamin B12 and folate levels

The results of the two samples *t*-test [Table 3] showed a significant difference in the mean B12 levels between those who had versus those who did not have a history of fracture (P = 0.044). There was no significant difference in the mean folate levels between these two groups (P =0.145).

Other factors associated with BMD, vitamin B12 and folate levels

BMD showed a significant positive correlation with body mass index (BMI) at the lumbar spine and femoral neck (P = 0.000). Moreover, the correlations of total BMD with age, gender, and postmenopausal status were highly significant, as shown in Table 4.

The multiple linear regression analysis results in Tables 5 and 6 show the possible influence of age, BMI, and B12 levels in predicting BMD. As per the β coefficients of linear regression analysis, BMI and age were the main predictors of BMD at the lumbar spine and femoral neck. Furthermore, there was no statistically significant correlation between vitamin B12 levels and the use of metformin (P =0.26).

Discussion

Prevalence of osteoporosis

Our subjects' ages were in the range of 20–103 years, and the prevalence of osteoporosis among the included population was 11%. An epidemiological analysis showed that 34% of healthy Saudi women and 30.7% of men aged 50–79 years are osteoporotic. [12] In our study, the higher prevalence of osteoporosis may be related to the higher age range in their population: The previous study youngest subject was 50 years old,[12] whereas our youngest subject was 20 years old. The lower prevalence of osteoporosis in our study seems to be explained by the significantly lower age range in our study population.

Prevalence of vitamin B12 and folate deficiencies

The prevalence of vitamin B12 deficiency among the included population was 8.3%, and the prevalence of folate deficiency was 1.3%, which is consistent with what was found in a previous study conducted in Saudi Arabia by Alharbi *et al.*,[13] where the prevalence of B12 deficiency was 7.8%. However, there was a significant variation found in international studies.

Table 2: Correlation between BMD, vitamin B12, and folate

	T-Lumbar	*P*	T-Femoral	*P*
Vitamin B12	-0.04	0.926	-0.14	0.070
Folate	-0.04	0.683	-0.02	0.79

BMD, bone mineral density

Table 3: Association of vitamin B12 and folate levels with fracture risk

History of fracture	*n*	Mean	Std. deviation	Std. error mean
B12 level *P*=0.044				
Yes	29	422.45	332.959	61.829
No	521	340.18	221.387	9.699
Folate level *P*=0.145				
Yes	12	1942.00	576.006	166.279
No	216	2217.93	980.772	66.733

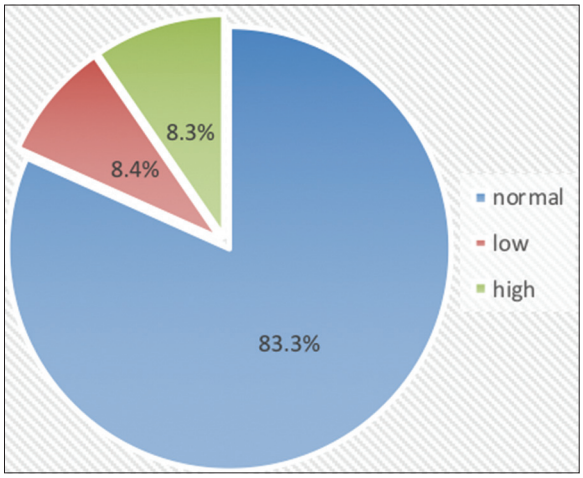

Figure 1: Vitamin B12 levels

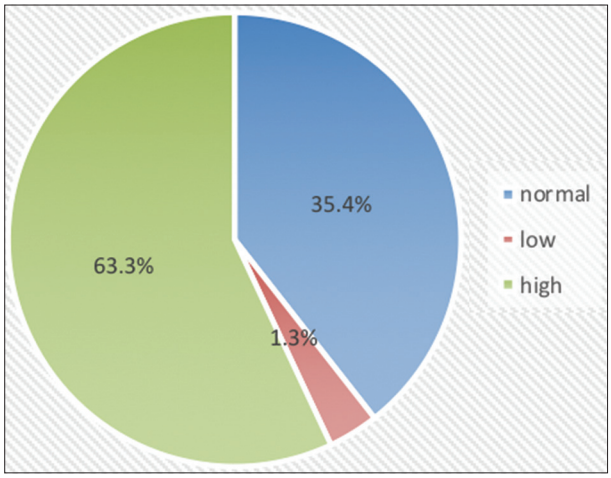

Figure 2: Folate levels

McLean *et al.*[14] reported that the prevalence rates of B12 deficiency were 31% and 12.4% of the elderly population in the United Kingdom and Canada, respectively, which is higher than that in our population. Conversely, the prevalence was 2.7% of the elderly population in the United States. Folate deficiency was reported as 29% in the elderly in the United Kingdom.[14] The reasons for this wide variance could be related to ethnic and sociocultural differences between societies and their varying dietary habits.[15]

Association between vitamin b12 and folate levels with fracture risk

In our study, a significant association was found between a history of fracture and the level of vitamin B12 but not the folate level. This is consistent with the findings of a previous study, which showed that low vitamin B12 levels were significantly associated with three times risk of fractures. The explanation for this could be related to the contribution of vitamin B12 in bone formation and osteoblast activity.[4,16] However, we are not aware of other than Dhonukshe-Rutten RA *et al.*'s study that observed and found a significant association between vitamin B12 levels and fracture risk. Therefore, more studies are suggested to explore and confirm our findings. In contrast, a separate study investigating plasma homocysteine, folate, vitamin B12, and the risk of hip fracture found that B12 was not a predictor for hip fracture, whereas folate was a predictor only among women.[16] Another study found no effect of vitamin B12 and folate supplementation in patients with low vitamin B12 and folate levels on fracture risk.[18]

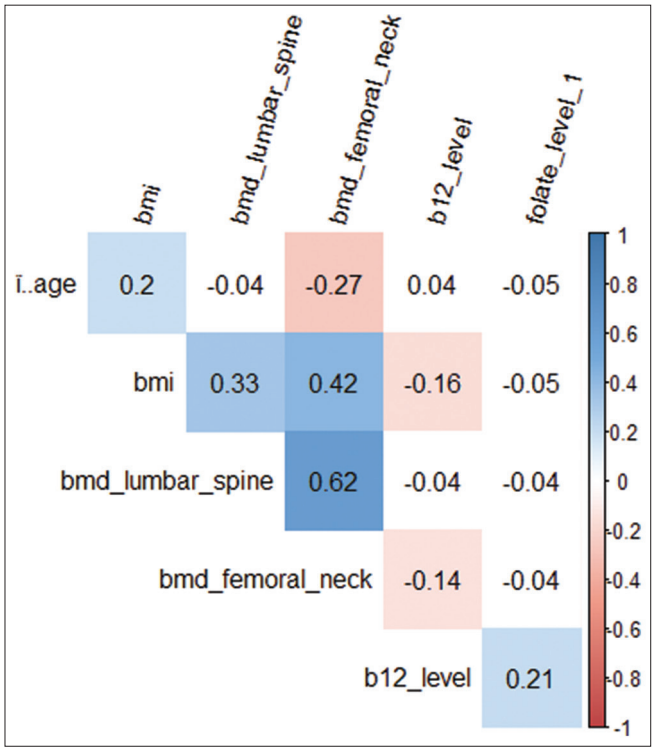

Figure 3: Heat map showing the bivariate correlation between pairs of variables

Association between vitamin b12 and folate levels with BMD

This study showed that low serum levels of vitamin B12 and folate were not associated with bone loss. These findings are in agreement with the findings of previous studies, which reported that vitamin B12 and folate levels were not related to BMD in postmenopausal women.[6,7] In contrast, a study conducted in Nigeria reported that vitamin B12 and folate deficiencies are associated with a reduction in BMD in osteoporotic patients, whereas other studies conducted in Morocco, the United States, and Turkey reported that vitamin B12 levels, but not folate levels, were associated with osteoporosis.[8-11] Two studies that investigated only vitamin B12 were conducted by Stone *et al.*[19] and Dhonukshe-Rutten *et al.*[20]; the authors of one study reported that low levels of vitamin B12 in older women are associated with hip bone loss, whereas the authors of the other found that low vitamin B12 levels were associated with osteoporosis. In another study, Cagnacci *et al.*[21] found that folate, but not vitamin B12, was related to BMD, and the findings suggested a major association between folate and bone mineralization. In the single local study conducted in Saudi Arabia, Alharbi *et al.*[3] considered only men. They found that vitamin B12 and folate levels may

Table 4: Correlations of total BMD with the specified parameters

Parameters	Kendall's tau	*P*
Age categories	0.164	0.00001**
Gender	0.133	0.001**
Smoking	0.053	0.206
B12 categories	0.028	0.486
Folate categories	0.007	0.951
Postmenopausal	0.169	0.0001**

**Highly significant correlation

Table 5: Multiple linear regression for BMD lumbar spine

Parameters	Regression coefficient	*P*
B12	0.001	0.001**
Folate	4.169	0.777
Age	-0.042	0.0001**
BMI	0.071	0.0001**
Postmenopausal	-1.138	0.6110
Smoking status	-0.274	0.133
R^2=0.28		

**Highly significant influence on the dependent variable. BMD, bone mineral density; BMI, body mass index

Table 6: Multiple linear regression for BMD femoral neck

Parameters	Regression coefficient	*P*
B12	0.001	0.427
Folate	0.000	0.209
Age	0.055	0.0001**
BMI	0.059	0.0001**
Postmenopausal	0.264	0.2400
Smoking status	0.013	0.929
R^2=0.255		

**Highly significant influence on the dependent variable. BMD, bone mineral density; BMI, body mass index.

indirectly affect BMD through their effects on homocysteine levels.[3] However, these primary findings are consistent with the results of a systematic review of 17 studies, in which only three studies found an association between vitamin B12 and BMD.[22] The causes of the discrepancies are not clear. However, some confounding factors that may have contributed include the methods used to diagnose B12 levels, such as investigating dietary intake of vitamin B12, plasma, or serum vitamin levels and the analysis of homocysteine and methylmalonic acid levels. In addition, the first two studies that found positive correlations were done on different populations, studying the relation in patients with pernicious anemia and celiac disease.[22-25] Our patient population was drawn from community-based family health clinics in Riyadh.

Other factors affecting vitamin B12, folate levels and BMD

Vitamin B12 deficiency because of drug use has been reported in several previous studies, especially in terms of metformin, which is used to treat diabetes mellitus type 2.[26,27] However, contrary to their findings, we did not find any association between metformin use and B12 deficiency, which is in line with Tarik Elhadd *et al.*,[28] who reported that B12 levels were comparable between metformin and nonmetformin users. The reason for this could be related to the dose of metformin or duration of use; as Alharbi *et al.*[13] reported, a local study found that low levels of vitamin B12 were only evident when metformin was taken at a dose of more than 2,000 mg/day for more than 4 years. BMD showed significant positive correlations with BMI values in both the lumbar spine and femoral neck. This is consistent with what has been found in previous studies.[3,29,30] Clearly, in a retrospective observational study like this, it was difficult to assess the extent of vitamin B12 and folic supplementation among our population. Accordingly, this parameter could affect the possible implications of the outcome of our study. Another issue is that it is not common to screen for osteopenia or osteoporosis in men in our primary care clinics; therefore, the male population might not give us an accurate normal range, potentially skewing our results to a higher prevalence of osteoporosis.

Conclusion

Vitamin B12 levels were associated with the risk of fracture, but vitamin B12 and folate levels did not correlate with BMD (femoral neck and lumbar spine).

Although Vitamin B12 and folate deficiencies can be preventable, more extensive studies should be conducted to establish the correlation between vitamin B12 and folate with BMD and the correlation between the risk of fractures and vitamin B12 levels.

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Conflicts of interest

There are no conflicts of interest.

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