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Research article

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Fib-4 Score as a Potential Indicator for Osteopenia: Insights from a Postmenopausal Cohort

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Abstract

Background: *Osteoporosis and osteopenia are significant health concerns, with risk factors including age, lifestyle, and metabolic disorders like fatty liver disease. This study investigated the association between the Fibrosis-4 (FIB-4) score and osteopenia among postmenopausal women while identifying predictive markers indicative of osteopenia.*

Material and Method: *A cross-sectional analysis involved 151 postmenopausal women, assessing their bone mineral density (BMD) using dual-energy X-ray absorptiometry. BMD values for lumbar and femur neck regions were noted. Hepatic ultrasonography, laboratory evaluations, and anthropometric assessments were performed. The FIB-4 score, indicating liver fibrosis risk, was calculated based on specific parameters.*

Results: *Participants had an age of 56.0 ± 6.4 years, with average. Osteopenia was observed in 28.5% (L1-L4) and 27.2% (femur neck) of participants. Significant correlations were found between osteopenia and markers such as ALP, AST, ALT, serum calcium, and vitamin D. The association between osteopenia and NAFLD by ultrasonography was significant in the femur neck 42.9% of women with intermediate FIB-4 scores (1.30-2.67) exhibited osteopenia at the lumbar vertebrae, compared to 21.6% with FIB-4 scores <1.3 (p=0.007). For the femur neck, 44.9% of women with intermediate FIB-4 scores had osteopenia versus 18.6% with FIB-4 scores <1.3 (p=0.001). Logistic regression revealed ALP (p=0.007, OR:1.1, 95%CI: 1.03-1.05) and FIB-4 score (p=0.005, OR:2.9, 95%CI: 1.38-6.48) as significant predictors for L1-L4 BMD. The FIB-4 score 1.3 demonstrated 93% sensitivity and 77% specificity for detecting osteopenia at L1-L4.*

Conclusion: *The study underscores a significant correlation between FIB-4 scores and osteopenia among postmenopausal women. Elevated FIB-4 scores and specific biochemical markers like ALP were identified as predictive markers for osteopenia.*

Keywords: Postmenopausal Women, Osteopenia, Osteoporosis, Fib4 Score, Bone Mineral Density, Fatty Liver Disease

1. Introduction

Osteoporosis is a bone mineral density (BMD) 2.5 or more SD below the mean of normal young women [1]. Osteoporosis was found to affect 11.4%, 24.8%, and 37.6% of individuals in the age groups of 50-59, 60-69, and 70-79, respectively, according to a meta-analysis. Bone density between 1 and 2.5 SD below the mean is called osteopenia [2]. This means a person with osteopenia does not yet have osteoporosis but is at risk of developing it if not treated. Osteoporosis was shown to lead to 3.5 million fragility fractures annually in Europe [3]. Underlying risks for osteoporosis are various, such as advanced age, long-term glucocorticoid therapy, low body weight (less than 58 kg), cigarette smoking, excess alcohol intake, and race/ethnicity [4].

One of the associated metabolic disorders for osteoporosis is chronic liver disease, where the prevalence of osteoporosis varies between 10-40% and higher than the normal population [5,6]. Non-alcoholic fatty liver disease (NAFLD), which may progress to cirrhosis, has been shown to be associated with many metabolic and anthropometric parameters [7]. The new definition of NAFLD is metabolic dysfunction-associated fatty liver disease (MAFLD), defined as patients with both hepatic steatosis and any of the three metabolic conditions—overweight/obesity, diabetes mellitus, or metabolic dysfunction, has become the most common chronic liver disease [8,9].

NAFLD/MAFLD in various ways, such as changes in transforming factors of bone metabolism, vitamin D levels, the chronic inflammatory state of the liver, hepatic fibrosis severity, and disruptions in lipid metabolism. These complex relationships have led to numerous scientific studies on the links between NAFLD and osteoporosis/osteopenia, but the conclusions have been controversial and not yet fully comprehended [10-15].

Several studies focused on the US population over 50, using cross-sectional analyses of the 2017-2018 National Health

and Nutrition Examination Survey, have discovered that liver steatosis and fibrosis are not independently connected with osteopenia or osteoporosis. However, these studies have also revealed that patients diagnosed with MAFLD have higher BMD compared to their controls [16-18]. In contrast, a separate cross-sectional study conducted in Rome, Italy, on 1,872 obese individuals found that an increased Fibrosis-4 (FIB-4) score, an index of liver fibrosis, was correlated with lower BMD and an elevated risk of osteopenia/osteoporosis [19].

In the ambit of this research, our primary objective was to assess the correlation between the FIB-4 score and osteopenia among postmenopausal women. Additionally, we endeavored to identify pivotal predictive markers indicative of osteopenia.

2. Material Method

In this cross-sectional analysis, we enrolled 151 women who had transitioned into the postmenopausal phase. These participants were in commendable general health conditions, defined by the absence of menstruation for a consecutive 12-month period. The evaluation encompassed a range of diagnostic procedures, such as dual-energy X-ray absorptiometry to gauge bone mineral density (BMD), hepatic ultrasonography assessments, as well as laboratory and anthropometric evaluations. Exclusions from the study criteria incorporated women with recent or consistent alcohol consumption (defined as a daily intake of up to 14 grams within the past three months), significant liver or kidney impairments, those undergoing or having undergone treatments involving estrogen, progesterone, glucocorticoids, or calcium supplementation, individuals with surgically induced menopause or premature menopause, and those with a family history of fragility fractures.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Blood samples were collected in the morning after at least 12 overnight fasting to measure fasting plasma glucose (FPG), vitamin D, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT).

FIB4 score was calculated using the formula: FIB-4 = age ([y] × AST [U/L])/((PLT [109/L]) × (ALT [U/L])1/2), FIB-4 score <1.3 defined as low risk, 1.3-2.67 as intermediate risk [20].

Dual-energy x-ray absorptiometry (DXA) was used to measure BMD and two sites were checked: total lumbar (L2–4) and femur neck. The results were categorized into two groups with respect to T score as normal ($T \geq -1.0$) and osteopenia ($-2.5 < T < -1.0$) [21].

3. Statistical Analysis

All statistical analyses were conducted using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Baseline characteristics were depicted as mean ± standard deviation (SD) for variables with a normal distribution, median (interquartile range) for those not adhering to a normal distribution, and frequencies with percentages for categorical data. Categorical variables underwent comparison through the chi-square test, while associations between continuous and categorical variables were evaluated using the Mann–Whitney U test. To ascertain the sensitivity and specificity of osteopenia prediction thresholds, a Receiver Operating Characteristic (ROC) analysis was executed. Furthermore, logistic regression was utilized to identify independent markers predictive of osteopenia.

4. Results

Our study involving 151 postmenopausal women observed an average age of 56.0 ± 6.4 years. The average height and weight of the participants were 164.3 ± 9.6 cm and 81.8 ± 13.3 kg, respectively. Additionally, the average daily dietary energy intake was 2066 ± 297 kcal, with a protein intake of 66.1 ± 4.3 g/day.

In terms of health history, 25.1% of participants had a history of smoking, and 25.2% had been diagnosed with diabetes.

The average BMD for the lumbar vertebrae (L1-L4) was 1.13 ± 0.19 mg/cm^2, while the femur neck was 1.02 ± 0.14 mg/cm^2. Analyzing the T-scores, most participants (71.5% for L1-L4 and 72.8% for the femur neck) had average scores. However, 28.5% showed osteopenia in the L1-L4 region and 27.2% in the femur neck.

Regarding liver function tests, 4.6% of participants had elevated AST levels, and 15.2% had elevated ALT levels, ranging between 1 and 2.5 times the upper limit of normal. Moreover, 3.3% exhibited elevated ALP levels.

The median corrected serum calcium level was 9.5 mg/dl, with levels ranging from 8.7 to 10.2 mg/dl. Serum phosphorus levels above 4.5 mg/dl were observed in 3.9% of participants. Notably, 27.1% of participants had serum vitamin D levels below the recommended 12 ng/mL threshold, with a median level of 18.5 ng/mL and a range from 3.0 to 74.8 ng/mL.

	Mean ± SD
Age	56,0 ± 6,4
Height (cm)	164,3 ±9,6
Weight (kg)	81,8 ± 13,3
Dietary energy intake kcal/day	2066 ±297
Dietary protein intake g/day	66,1 ±4,3
L1-L4 BMD (mg/cm2)	1,13 ±0,19
Femur total BMD (mg/cm2)	1,02 ±0,14

Table 1: Mean ± standard deviation values of the parameters with normal distribution

	N=151	%
Smoking History	36	25.1
Diabetes History	38	25,2
L1-L4 T score Normal Osteopenia	 108 43	 71.5 28.5
Femur total T score Normal Osteopenia	 110 41	 72.8 27.2
FIB4 score low risk: <1.3 intermediate risk: 1.3-2.67	 102 49	 67.5 32.5
BMI 18,5-24,9 25,0-29,9 30,0-34,9	 16 47 57	 10,6 31,1 37,7
AST median 18.0 U/L (range: 10.4-54.0) 1-2.5 x ULN	 7	 4,6
ALT median 19.0 U/L (range:5.8-79.0) 1-2.5 x ULN	23	15,2
ALP median 77 U/L (range: 19-186) 1-2.5 x ULN	5	3.3
Serum Vitamin D median 18.5 ng/ml (range:3.0-74.8)	-	-
Serum Phosphorus median 3,6 mg/dl (range: 2.4-5.0) > 4,5 mg/dl	6	3.9
Serum Vitamin D median 18.5 ng/ml (range:3.0-74.8) < 12 ng/mL	41	27.1

Table 2: Patient characteristics

Osteopenia in the femur neck was significantly correlated with ALP, AST, ALT, serum Calcium, and vitamin D (all p values <0.05). However, age, BMI, fasting blood glucose, GGT, dietary protein, and energy intake were not significantly associated with osteopenia.

The association between osteopenia and NAFLD by ultrasonography was insignificant in the L1-L4 region. However, it was significant in the femur neck (p=0,02). 36 (34.3%) of women with grade 2/3 steatosis had osteopenia, while 4 (9.1%) women with grade 0/1 steatosis had osteopenia in the femur neck.

Osteopenia in L1-L4 was significantly linked to BMI, vitamin D, ALP, and AST (all p values <0.05). There was no significant correlation between osteopenia and age, fasting blood glucose, GGT, ALT and dietary protein, and energy intake.

22 (21.6%) out of 102 women with FIB4 score <1.3 had L1-L4 osteopenia, while 21 (42.9%) out of 49 women with intermediate FIB4 score (1.30-2.67) had osteopenia (p=0.007) (Fig1). 19 (18.6%) out of 102 women with FIB4 score <1.3 had osteopenia in femur neck, while 22 (44.9%) out of 49 women with intermediate FIB4 score (1.30-2.67) had osteopenia in femur neck (p=0.001) (Fig2).

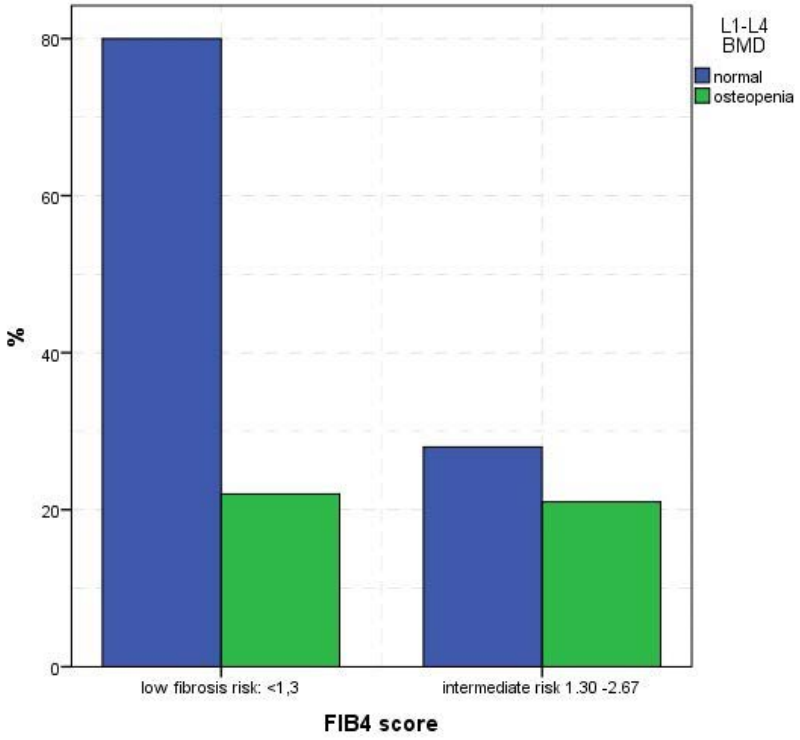

Figure 1: The relationship between FIB4 score and L1-L4 BMD

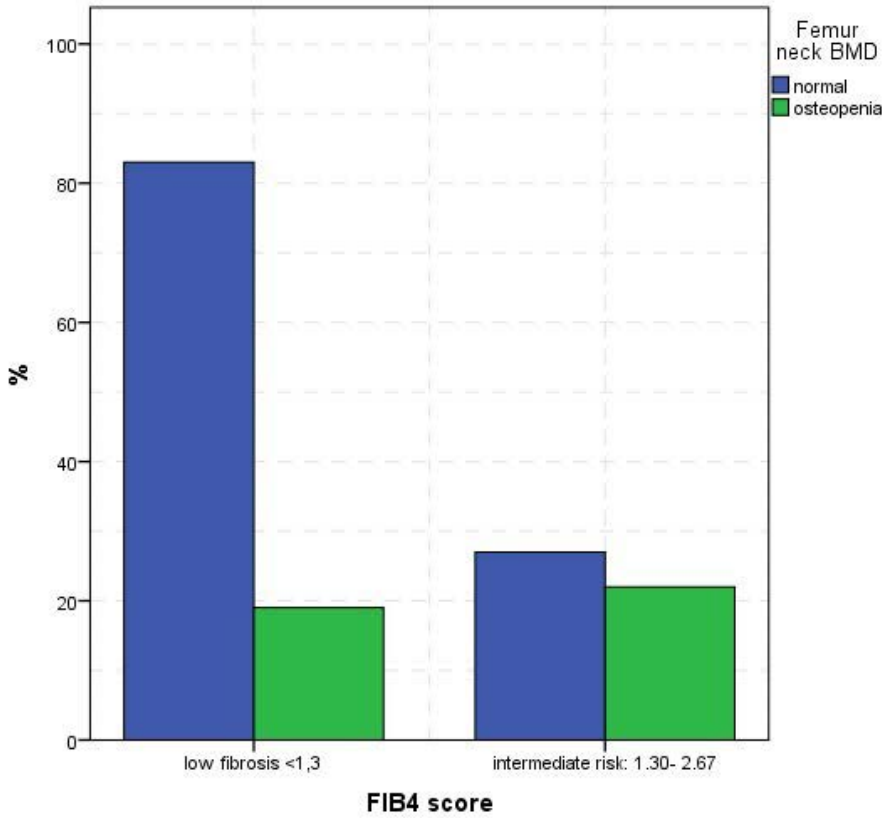

Figure 2: The relationship between FIB4 score and Femur neck BMD

Binary logistic regression analysis indicated that significant predictive markers for L1-L4 BMD were ALP (p=0.007, OR:1,1, 95%CI: 1,03-1,05) and FIB4 score (p=0.005, OR:2.9, 95%CI 1,38-6,48) (Table3).

L1-L4 Bone Mineral Density					
Factors	***Coefficient β***	***Wald X_2***	**p**	**OR**	**95% CI**
Serum corrected Calcium	0,56	1,03	0,3	1,7	0,59-5.26
Vitamin D	-001	0,01	0,9	0,9	0,97-1,02
ALP	0,19	7,2	0,007	1,1	1,03-1,05
FIB4 score	1,09	7,7	0,005	2,9	1,38-6,48
BMI	-0,5	0,55	0,4	0,11	0,26-3,64
Femur Bone Mineral Density					
Factors	***Coefficient β***	***Wald X_2***	**p**	**OR**	**95% CI**
Serum corrected Calcium	0,1	0,11	0,7	1,2	0,39-3,76
Vitamin D	-0,02	2,25	0,1	0,97	0,94-1,007
ALP	0,01	2,2	0,1	1,0	0,99-1,02
FIB4 score	1,2	0,39	0,001	3,6	1,67-7-87

Table 3. Binary logistic regression analysis of predictive markers for osteopenia

The ROC analysis determined the sensitivity and specificity for the FIB 4 score cut-off value of 1.3. The roc curve did not show a significant cut-off value for femur neck osteopenia, while 1,3 was significant for L1-L4 osteopenia (p=0.004, AUC: 0,39, 95%CI 0,29-0,49). FIB4 score 1.3 had 93% sensitivity and 77% specificity for detecting osteopenia (Fig3).

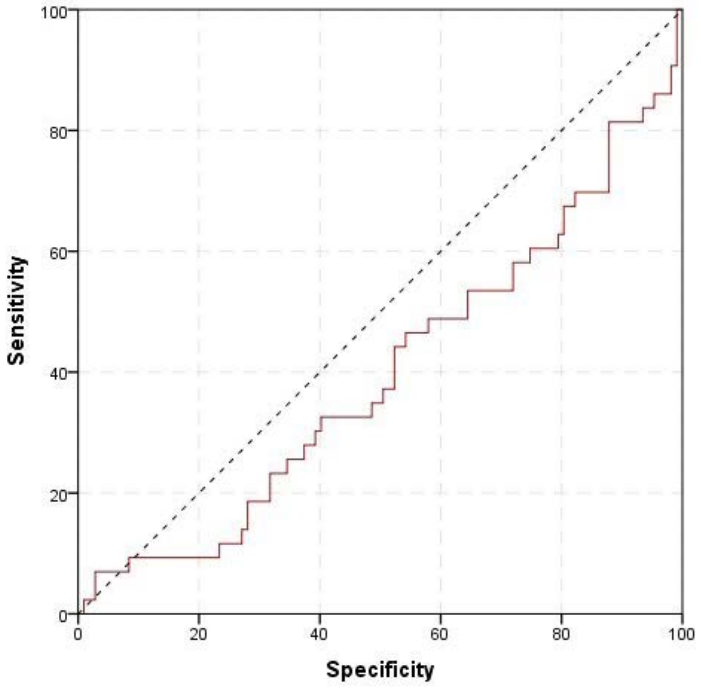

Figure 3: The ROC curve of sensitivity and specificity for 1.3 FIB4 score predicting osteopenia

5. Discussion

Both osteoporosis and NAFLD/MAFLD are an increasing healthcare problem worldwide. Hence, analyzing possible predictive markers is crucial in detecting these conditions earlier and preventing morbidities related to these diseases.

There have been various discussions about the possible causes of NAFLD and osteoporosis (5-7). These include vitamin D deficiency, increased cytokines from the inflamed liver, limited physical activity, and others [14].

Recently, a study by Zhang et al. demonstrated a significant correlation between FIB-4 score and elevated risk of osteoporosis (OR:1.44, p-value = 0.013). The results of the multivariable regression analyses, which considered potential confounding variables including body mass index, revealed no statistically significant associations between hepatic steatosis and fibrosis indices with BMD and the risk of osteopenia/osteoporosis [22].

In a retrospective cross-sectional analysis involving 3,739 postmenopausal women, Lee et al [23]. discovered a notable inverse link between non-alcoholic fatty liver disease (NAFLD) and bone mineral density (BMD) after accounting for potential confounding factors. A recent meta-analysis comprising seven observational studies reached a parallel conclusion [10]. Pan et al. demonstrated in their analysis that individuals with NAFLD

face an elevated risk of osteoporosis (OR = 1.33, 95%CI: 1.24-1.44) and osteoporotic fractures (OR = 1.57, 95%CI: 1.08-2.29) (12). However, upon adjusting parameters, this significant association was observed solely in men, not women [10].

In a recent National Health and Nutrition Examination Survey (NHANES) investigation, Xie et al. identified a negative link between NAFLD and osteoporosis [24]. Nevertheless, this correlation lost significance after accounting for various covariates, including gender, age, race, poverty income ratio (PIR), and BMI. Consistent findings were reported in another NHANES study involving 1784 participants over 50 by Ciardullo et al. (16). A review concluded NAFLD patients have a higher risk of osteoporosis but not fracture and falling risk [25].

Our study on postmenopausal women's bone health reveals consistent patterns with previous research, particularly in the context of the relationship between non-alcoholic fatty liver disease (NAFLD) and osteopenia. Similar to Zhang et al.'s findings on the correlation between FIB-4 score and osteoporosis risk, our study identifies FIB4 score as a significant predictor for lumbar spine (L1-L4) osteopenia (p=0.005, OR:2.9, 95%CI 1.38-6.48).

Our observations align with studies by Lee et al., Pan et al., and Xie et al., demonstrating that while the association between NAFLD and osteopenia is insignificant in the L1-L4 region, it becomes significant in the femur neck (p=0.02). This mirrors the gender-specific trends highlighted by Pan et al., with our study emphasizing the significance of this association in postmenopausal women.

Compared to Ciardullo et al.'s work on NAFLD and osteoporosis, our study adds depth by exploring region-specific associations, emphasizing the importance of femur neck measurements in capturing NAFLD's impact on bone health.

Our results not only confirm existing evidence but also provide novel insights into the predictive role of specific markers, such as ALP and FIB4 score, in assessing the risk of osteopenia in distinct skeletal regions.

Several limitations of our study include a small sample size and retrospective design. Moreover, in this study, participants had osteopenia and low or high FIB-4 score. Due to the cross-sectional design of the study, it is difficult to determine the cause-and-effect relationship or the chronological sequence of events.

6. Conclusion

In summary, our study shows how NAFLD, along with FIB4 score and ALP, affects osteopenia in postmenopausal women. We found these factors to be crucial predictors, especially in specific regions of the body. Despite some study limitations, our results provide practical insights into potential markers for diagnosing osteopenia and highlight the importance of considering different body areas. This research adds to what we know about how metabolic issues impact bone health, paving the way for more exploration in this area and emphasizing the need for comprehensive approaches to tackle NAFLD and osteopenia in postmenopausal women.

Acknowledgments

Statement of Ethics: Written informed consent was obtained from all participants. The Local Ethics Committee of Istanbul Medipol University approved the study in November 2023 with decision number E-10840098-772.02-7194.

Conflict of interest: The authors declare no conflict of interest.

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