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Original Article

Predictors of Low Bone Mineral Density in a Cohort of Egyptian Multiple Sclerosis Patients

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Abstract

Background: Multiple sclerosis (MS) is an autoimmune disease accompanied by release of inflammatory cytokines, which induce osteoclastogenesis affecting bone metabolism, causing osteoporosis (OP). However, OP in MS patients is multifactorial. The purpose of this study was to examine the prevalence of aberrant bone mineral density (BMD) and its correlation with demographic and clinical variables in MS patients, investigating the role of vitamin D (VD) levels and determining predictors of aberrant BMD.

Methods: This cross-sectional study enrolled 124 patients. Disability and severity scores, along with MRI brain results, were documented. Levels of 25 (OH) cholecalciferol, parathyroid hormone, and serum calcium were recorded. Using dual-energy X-ray absorptiometry, BMD was determined.

Results: 120 patients were identified with VD deficiency. 56.5% exhibited reduced BMD in the spine, and 54.8% showed decreased BMD in the femur. Negative correlation was detected between VD and frequency of relapses over the preceding two years. Additionally, femoral Z-scores were negatively correlated with age, disease duration, total serum calcium levels, disability and severity scores. Significant relationships were found between the Z-scores of the forearm, femur, and spine and the overall lesion load. Multivariate logistic regression revealed an independent correlation between the incidence of relapses in the past two years and low BMD

Conclusions: High prevalence of low BMD is seen in MS patients. More than half exhibiting reduced BMD. VD deficiency was frequently observed and correlated with an increased number of relapses. Patients are more likely to have low BMD if they had more relapses in the previous two years.

Keywords: Multiple sclerosis; Bone mineral density; Predictors; Vitamin D; Egyptian

INTRODUCTION

As an autoimmune disease, MS is accompanied by the release of multiple inflammatory cytokines, which induce osteoclastogenesis and affect bone metabolism, causing osteoporosis (OP)[1]. However, OP in MS patients is multifactorial. Factors such as vitamin D (VD) deficiency, mobility limitation, muscular dysfunction, dysautonomia, and immunomodulatory agents, including corticosteroids, all contribute to OP and abnormal bone metabolism in MS patients [2].

It's unclear what the particular reason of MS is. However, several environmental and genetic factors have been linked to its pathogenesis, including serum VD levels [3], VD receptor polymorphisms (VDP) [4], and the sun exposure [5]. More findings indicate that VD deficiency may influence

progression and outcomes of the disease. [6]. VD is thought to be a powerful immunomodulator that can reduce the risk of MS, reduced relapse rates, and improve disease outcomes [7].

The study aims at assessment of the degree of prevalence of abnormal bone mineral density (BMD), and its relation to various demographic and clinical parameters in Egyptian MS patients as well as to predict abnormal BMD. The second aim is to conduct an inquiry about the association between VD levels and various disease activity parameters in an entourage of Egyptian MS patients.

METHODS

Our cross-sectional study was during the period from January 2023 to March 2024 in the Neurology Department, Kafrelsheikh University Hospitals. 124 patients were included in the study. Their ages ranged from 18 to 50 years. They were diagnosed as clinically defined MS according to the 2017 McDonald criteria [8]. The exclusion criteria included smoking, a history of secondary osteoporosis, ongoing pregnancy or lactation, renal disorders, bone marrow dysfunction, hypercalcemia, and certain circumstances, such as lumbar spinal fusion surgery, that complicate dual-energy X-ray absorptiometry (DEXA). The current study was approved by the local ethical committee at Kafrelsheikh University with the approval code KFSIRB200-248 at 27-5-2024. All patients were provided an informed consent to participate.

Every patient underwent a comprehensive history-taking and clinical assessment. Data collected included disease onset, duration in years, the total number of relapses, and number of relapses in the last two years, and current disease-modifying treatment (DMT). MS patients were assessed for osteoporosis risk and bone pain history at the Rheumatology Department, Kafrelsheikh University Hospital. Details of steroid intake, including the type of steroid (intravenous methylprednisolone as pulse therapy during attacks or oral prednisolone) and the duration of steroid use, were recorded.

The MS patients were categorized into two groups according to their clinical course: relapsing-remitting (RRMS) and progressive MS (including primary and secondary progressive MS). Clinical disability was assessed using expanded disability status scale (EDSS) [9], while MS severity was assessed using multiple sclerosis severity scale (MSSS), an algorithm that correlates EDSS scores with comparable disease durations in MS patients [10].

MRI of the brain and cervical and dorsal spine with contrast was conducted using a 3.0 T MRI (Philips Ingenia 3.0T MRI-scanner, Philips Healthcare, Netherlands) and a standard head and neck coil. The imaging sequences included:

- 3D T1-weighted Magnetization Prepared – Rapid Acquisition Gradient Echo (MPRAGE) [TR = 900 ms, TE = 4.43 ms, flip angle = 90°, 1.2 mm isotropic spatial resolution]
- 2D FSE T2-weighted images [TR = 2000 ms, TE = 60 ms, flip angle = 90°]
- 3D Fluid-Attenuated Inversion Recovery (FLAIR) (TR = 8210 ms, TE = 100 ms, TI = 2500 ms, 1.5 × 1.5 × 4 mm spatial resolution)
- T1-weighted images [TE = 2.5 ms, TR = 225 ms, FOV = 220 mm, slice thickness = 3 mm, voxel size = 0.7 × 0.7 × 3.0 mm]
- Post-contrast T1 with fat suppression in axial, coronal, and sagittal planes [TR = 700 ms, TE = 4.43 ms, flip angle = 90°, in axial, coronal, and sagittal planes]

MRI lesions were assessed for lesion load (defined as nine or more lesions), lesion enhancement indicating disease activity, and black holes indicating axonal loss [11].

The BMD was measured at the L2-L4 lumbar spine (postero-anterior projection), the left femoral neck, and the distal forearm using DEXA with a DPX alpha machine (Lunar Corporation, USA). DEXA results were expressed as BMD (g/cm²) and as the Z-score, an important indicator for evaluating BMD via DEXA scans [12,13]. This score measures an individual's BMD relative to the average BMD of a reference group matched for age, sex, and ethnicity, represented in standard deviations from the mean. A Z-score of 0 signifies that the BMD is equivalent to the reference population's average. Positive Z-scores denote higher BMD, while negative scores indicate lower BMD. In clinical practice, a Z-score of -2.0 or lower signifies low BMD below the expected range for age, necessitating further examination for potential secondary osteoporosis or other underlying conditions that may affect bone health [14]. The International Society for Clinical Densitometry (ISCD) advises the use of Z-scores for premenopausal women, men under 50, and children, as these scores offer a more appropriate assessment of bone health in younger populations, where age-related bone loss is less prevalent [15].

Total and ionized serum calcium levels were determined using an automated chemistry analyzer (Cobas C311, Roche Diagnostics, Germany)(Reference ranges 8.5-10.2 mg/dL and

1.10-1.35 mmol/L respectively). The chemiluminescence immunoassay (CLIA) method on a fully automated analyzer (Immulite 1000, Siemens, or Cobas e411, Roche Diagnostics, Germany) was used to measure levels of parathyroid hormone (PTH)(reference range 10-65 pg/mL) and serum vitamin D with reference range 30-100 ng/mL

Statistical Analysis

Data were analyzed using SPSS version 20.0. Data were reported as frequencies and percentages, range, mean with standard deviation, or median with interquartile range (IQR). Variables were compared by Student's t-test and Mann-Whitney U test. Spearman rank correlation was considered. Statistical significance was set at $p< 0.05$.

RESULTS

124 MS patients were enrolled with the percentage of males was 45.2% (56 patients), while that of females was 54.8% (68 patients). The median age of MS patients was 33 years. The median age of disease onset was 25 years (ranging from 20 to 30 years), and the median disease duration was 5.5 years (ranging from 3.0 to 10.0 years). Regarding the type of MS, 104 patients had RRMS, while 20 had progressive MS (18 with SPMS and 2 with PPMS). The median scores for the EDSS and the MSSS were 2.5 and 4.6, respectively. Ninety-one patients reported bone aches. The median number of relapses in the last 2 years was 2, while the median total number of relapses throughout the disease was 4.5.

Radiological data showed that 50 patients (40.3%) had a low lesion load, while 74 patients had a high lesion load. Sixty-six patients (53.2%) showed activity (enhancement) on MRI imaging, and black holes were present in 69 patients (55.6%). One hundred and twelve patients were on DMT. The most used DMTs were interferon (IFN) and fingolimod (FINGO), while rituximab was the least used. Twelve patients had not yet received treatment, either due to patient consideration or because they were recently diagnosed and had not started treatment by the time of sample collection (Table 1).

One hundred twenty patients had VD deficiency, while all patients had normal PTH serum levels. One hundred sixteen patients had normal total serum calcium levels, while only 76 patients had normal ionized calcium levels. In terms of BMD, 70 patients (56.5%) had low BMD in the spine, and 68 patients (54.8%) had low BMD in the femur, as indicated by the Z-scores (Table 1).

122 patients of the study participants received pulse steroid therapy, while 79% used oral steroids, with the duration of use detailed in Table 3. There was a statistical correlation between oral steroid use and VD levels, as well as the Z-scores of the spine and femur. Additionally, there was a statistical association between pulse steroid use and total calcium levels, ionized calcium levels, and the Z-scores of the femur and spine (Table 1).

Table 2 shows the correlation between laboratory values and various clinical parameters. There was a negative statistical correlation between VD serum levels and the number of relapses in the last 2 years. Moreover, disease duration and severity were negatively correlated with ionized serum calcium levels. The Z-score of the femur was negatively correlated with age, disease duration, ionized and total serum calcium levels, EDSS, and MSSS scores. The Z-score of the spine had similar results, except for the EDSS, where no correlation was found (Table 3). A statistical relationship was observed between the Z-scores of the forearm, femur, and spine on one side, and lesion load on the other side, as well as between the Z-score of the femur and the presence of black holes on MRI (Table 4).

Based on the univariate analysis, disease duration, age, total number of relapses, number of relapses in the last 2 years, high lesion load, and low VD level were statistically noteworthy determinants of low BMD. Multivariate logistic regression analysis revealed that the number of relapses in the last 2 years was independently associated with low BMD (Table 5).

Table (1): Distribution of the studied patients according to demographic data, principal disease characteristics, radiological findings, laboratory data and BMD (n = 124)

		No(%)
	Sex	
	Male	56 (45.2%)
	Female	68 (54.8%)
	Age	
	Min. – Max.	18.0 – 50.0
	Mean ± SD.	33.1 ± 7.9
Demographic data	Median (IQR)	33.0 (26.0 – 39.0)
	Marital status [Married]	92 (74.2%)
	Age of onset	
	Min. – Max.	15.0 – 48.0
	Mean ± SD.	26.0 ± 6.9
	Median (IQR)	25.0 (20.0 – 30.0)
	Disease Duration	
	Min. – Max.	1.0 – 24.0
	Mean ± SD.	7.2 ± 5.9
	Median (IQR)	5.5 (3.0 – 10.0)
	Total no of relapses	
	Min. – Max.	1.0 – 12.0
	Mean ± SD.	5.2 ± 2.9
	Median (IQR)	4.5 (3.0 – 7.50)
Clinical data	***No of relapses in last 2 years***	
	Min. – Max.	0.0 – 4.0
	Mean ± SD.	1.9 ± 0.8
	Median (IQR)	2.0 (1.0 – 2.0)
	Type of MS	
	RRMS	104 (83.9%)
	SPMS	18 (14.5%)
	PPMS	2 (1.6%)
	EDSS	
	Min. – Max.	1.0 – 8.0
	Mean ± SD.	2.8 ± 1.2
	Median (IQR)	2.5 (2.0 – 3.0)
	MSSS	
	Min. – Max.	0.6 – 9.6
	Mean ± SD.	4.7 ± 2.3
	Median (IQR)	4.6 (2.87 – 6.10)
	Complaint of bone ache	91 (73.4%)
	DMT	
	No	12 (9.7%)
	INF	48 (38.7%)
	DMF	6 (4.8%)
	FINGO	46 (37.1%)
	Siponimod	4 (3.2%)
	Natalizumab	6 (4.8%)
	Rituximab	2 (1.6%)

	Pulse steroid(taken) Min-Max(days) Median (IQR) *oral steroid(taken)* Min-Max(days) Median (IQR)	122 (98.4%) 5.0 – 34.0 5.0 (5.0 – 7.0) 98 (79%) 14.0 – 30.0 14.0 (14.0 – 14.0)
	Lesions load	
	Low	50 (40.3%)
	High	74 (59.7)
Radiological data	Activity (enhancement)	66 (53.2)
	Black holes	69 (55.6)
	Serum Vitamin-D	
	Normal (30:100)	4 (3.2%)
	Deficiency <30	120 (96.8%)
	Min. – Max.	7.0 – 32.0
	Mean ± SD.	15.5 ± 5.8
	Median (IQR)	14.3 (11.70 – 18.0)
Lab data	***PTH***	
	Abnormal	0 (0.0%)
	Normal (15:65)	124 (100.0%)
	Min. – Max.	10.9 – 63.6
	Mean ± SD.	33.5 ± 10.3
	Median (IQR)	32.5 (29.0 – 40.70)
	Total Serum Ca	
	Abnormal	8 (6.5%)
	Normal (8.1:10.4)	116 (93.5%)
	Min. – Max.	7.9 – 11.1
	Mean ± SD.	9.2 ± 0.6
	Median (IQR)	9.1 (8.80 – 9.86)
	Ionized Serum Ca	
	Abnormal	48 (38.7%)
	Normal (1.16:1.31)	76 (61.3%)
	Min. – Max.	1.0 – 1.9
	Mean ± SD.	1.2 ± 0.1
	Median (IQR)	1.2 (1.10 – 1.25)
	T score Spine	
	Osteoporosis (<-2.5)	12 (9.7%)
	Osteopenia (-1:-2.5)	58 (46.8%)
	Normal (>-1)	54 (43.5%)
	Min. – Max.	-4.2 – 3.0
	Mean ± SD.	-1.0 ± 1.4
	Median (IQR)	-1.2 (-2.0 – -0.10)
BMD	***T score femur***	
	Osteoporosis (<-2.5)	24 (19.4%)
	Osteopenia (-1:-2.5)	44 (35.5%)
	Normal (>-1)	56 (45.2%)
	Min. – Max.	-4.5 – 3.0
	Mean ± SD.	-1.0 ± 1.6
	Median (IQR)	-1.2 (-2.40 – 0.20)

IQR: **Inter quartile range** SD: **Standard deviation**
Min : Minimum , Max : maximum , RRMS :Relapsing remittent Multiple Sclerosis , SPMS : Secondary progressive Multiple Sclerosis , PPMS :Primary Progressive Multiple Sclerosis , EDSS: Expanded disability status scale , MSSS: Multiple Sclerosis Severity Scale , INF : Interferon beta, DMF : Dimethyl Fumarate, Fingo: Fingolimod, BMD : Bone Mineral Density

Table (2): Correlation between laboratory data / DEXA scan data and duration of steroid intake (pulse and oral steroid)

	Duration of Pulse (days) (n = 122)		Duration of Oral (days)(n = 98)	
	r_s	p	r_s	p
Serum Vitamin-D	-0.173	0.056	-0.317*	0.001*
PTH	0.171	0.060	-0.060	0.557
Total Serum Ca	-0.213*	0.019*	0.075	0.461
Ionized Serum Ca	-0.220*	0.015*	-0.074	0.471
Z score FA	0.115	0.208	0.187	0.065
Z score Spine	-0.235*	0.009*	-0.313*	0.002*
Z score femur	-0.196*	0.031*	-0.324*	0.001*

r_s: **Spearman coefficient**
*: Statistically significant at $p \leq 0.05$
DEXA: Dual-Energy X-ray Absorptiometry , PTH : Parathyroid Hormone, Ca : Calcium ,Z score FA: Z score Forearm

Table (3): Correlation between laboratory data and different clinical parameters (n = 124)

	Laboratory							
	Serum Vitamin-D		PTH		Total Serum Ca		Ionized Serum Ca	
	r_s	p	r_s	p	r_s	p	r_s	p
Age	-0.160	0.076	0.140	0.120	-0.087	0.335	-0.132	0.142
Disease duration	0.052	0.570	-0.053	0.560	-0.026	0.775	-0.198*	0.027*
Total number of relapses	0.077	0.398	-0.007	0.941	-0.109	0.227	-0.102	0.260
Number of relapses in the last 2 years	-0.292*	0.001*	-0.029	0.746	-0.084	0.356	-0.149	0.098
EDSS	0.041	0.652	-0.021	0.818	-0.029	0.751	-0.080	0.377
MSSS	-0.021	0.816	0.061	0.501	-0.195*	0.030*	-0.261*	0.003*

r_s: **Spearman coefficient**
*: Statistically significant at $p \leq 0.05$
PTH: Parathyroid Hormone, EDSS: Expanded disability status scale , MSSS: Multiple Sclerosis Severity Scale

Table (4): Correlation between DEXA and different clinical parameters of MS patients (n = 124)

	DEXA					
	Z score FA		Z score Spine		Z score femur	
	r_s	p	r_s	p	r_s	p
Age	-0.346*	<0.001*	-0.268*	0.003*	-0.261*	0.003*
Disease duration	-0.398*	<0.001*	-0.292*	0.001*	-0.494*	<0.001*
Total number of relapses	-0.364*	<0.001*	-0.295*	0.001*	-0.456*	<0.001*
Number of relapses in the last 2 years	-0.196*	0.029*	-0.333*	<0.001*	-0.325*	<0.001*
EDSS	-0.047	0.602	-0.136	0.132	-0.186*	0.039*
MSSS	-0.385*	<0.001*	-0.248*	0.005*	-0.291*	0.001*

r_s: **Spearman coefficient**
*: Statistically significant at $p \leq 0.05$
DEXA: Dual-Energy X-ray Absorptiometry Z score FA: Z score Forearm, EDSS: Expanded disability status scale , MSSS: Multiple Sclerosis Severity Scale

Table (5): Relation between radiological data of MS and DEXA (n = 124)

	Lesions load		**Activity (enhancement)**		**Black holes**	
	Low (n = 50)	**High (n = 74)**	**Absent (n = 58)**	**Present (n = 66)**	**Absent (n = 55)**	**Present (n = 69)**
Z score FA						
Min. – Max.	-2.00 – 1.20	-6.10 – 3.20	-2.30 – 1.10	-6.10 – 3.20	-2.20 – 3.20	-6.10 – 2.90
Median (IQR)	-0.35 (-0.90 – 0.70)	-1.10 (-2 – -0.40)	-0.80 (-1.10 – 0.10)	-0.90 (-1.60 – 0.70)	-0.80 (-1.10 – 0.40)	-1 (-1.60 – 0.30)
(p)	**(p<0.001*)**		**(p=0.984)**		**(p=0.213)**	
Z score Spine						
Min. – Max.	-2.40 – 1.80	-4.20 – 3	-2.90 – 3	-4.20 – 2	-2.90 – 3	-4.20 – 2
Median (IQR)	-0.65 (-1.30 – 0.10)	-1.90 (-2.40 – -0.30)	-1.10 (-1.80 – -0.10)	-1.30 (-2.30 – -0.10)	-1.20 (-1.65 – 0.0)	-1.30 (-2.30 – -0.10)
(p)	**(p<0.001*)**		**(p=0.135)**		**(p=0.132)**	
Z score femur						
Min. – Max.	-3.10 – 1	-4.50 – 3	-3.10 – 2.50	-4.50 – 3	-3.80 – 3	-4.50 – 3
Median (IQR)	-0.35 (-1.20 – 0.70)	-1.95 (-2.60 – -0.40)	-1.10 (-1.90 – -0.10)	-1.40 (-2.60 – 0.20)	-1.10 (-1.75 – 0.70)	-1.40 (-2.60 – -0.30)
(p)	(p<0.001*)		(p=0.266)		(p=0.014*)	

IQR: **Inter quartile range** SD: **Standard deviation** **t: Student t-test**
U: Mann Whitney test
p: p value for Relation between DEXA with gender and type of MS
*: Statistically significant at $p \leq 0.05$
DEXA: Dual-Energy X-ray Absorptiometry ,Min: Minimum , Max : Maximum ,Z score FA: Z score Forearm

DISCUSSION

Osteoporosis is often overlooked as a comorbidity in multiple sclerosis, contributing to higher rates of illness and mortality. Early identification of patients at risk is critical because effective preventive therapy is currently available. The current research evaluated the prevalence of low BMD in a cohort of Egyptian MS patients and its associated predictors.

In this study, 96.8% of the studied patients had deficient VD levels, supporting that VD deficiency is very frequent between MS patients. This result is higher than a previous Egyptian study, which documented that 88.4% of MS Patients had low or insufficient amounts of vitamin D. [16]. Charabati et al. also highlighted low VD status, mostly due to insufficient sun exposure, as a significant environmental risk factor for MS, whereas adequate VD levels, particularly during early life, provide protective effects against disease onset [17]. VD's protective role is attributed to its involvement in immune and central nervous system cell proliferation and differentiation as Vitamin D mitigates this imbalance by inhibiting T-cell differentiation into TH17 cells through downregulation of IL-17, IL-22, RORC, and IL-23R genes, while promoting Treg cell production by upregulating FOXP3, IL-10, and CTLA4 genes [18].

On evaluation of BMD in MS patients, we used Z-scores of the femur, lumbar spine, and forearm, with low BMD observed in 54.8%, 56.5%, and 46.8% of patients, respectively. The BMD at the lumbar spine was found to be less in a study involving thirty-one men and women with MS than in controls, but it did not decrease at the femoral neck [19]. In contrast, BMD was affected more at the femur than the

lumbar spinein 80 hospitalized female MS patients [20].

According to self-reported data, the prevalence of OP in MS ranges from 5% to 29%. [21]. In a study of 142 women for BMD screening, 20.4% had osteoporosis [22]. Low BMD in MS patients arises from several interconnected factors. Reduced physical activity due to MS-related muscle weakness, spasticity, and fatigue limits weight-bearing exercises essential for bone health, accelerating bone loss. VD deficiency, which is frequent in MS patients due to reduced exposure to sun and altered metabolism, impairs calcium absorption and weakens bones. Long-term use of corticosteroids further depletes bone density. Chronic inflammation in MS disrupts normal bone remodeling processes, contributing to reduced BMD. Hormonal imbalances, such as altered levels of estrogen and testosterone, also accelerate bone loss, increasing the risk of osteoporosis. Simonsen et al found that 74.7% of MS patients had poor BMD after 10 years of onset, a figure much higher than the current finding due to the longer duration of disease as an inclusion criterion in their research [23]. However, Moen et al stated that even early MS is associated with significant bone mass deficits [24].

In the current work, there was a negative statistical correlation between oral steroid use and VD levels, Z-scores of the spine and femur, as well as a statistical correlation between pulse steroid use and total calcium level, ionized calcium level, and Z-scores of the spine and femur. Corticosteroids are essential in managing MS due to their anti-inflammatory properties, yet their prolonged use is associated with significant adverse effects, notably a reduction in BMD, leading to osteoporosis and increased fracture risk. These drugs impair osteoblast function, enhancing osteoclast activity, reducing new bone formation, and increasing bone resorption. Additionally, corticosteroids disrupt calcium homeostasis by decreasing gastrointestinal absorption and increasing renal excretion, and they lower levels of crucial sex hormones like estrogen and testosterone [25]. Many researchers have highlighted a greater frequency of osteoporosis and osteopenia in MS patients on corticosteroids, although other studies showed inconsistent results, likely due to varying administration and dosages [26,27]. Chronic systemic low-dose corticosteroid use necessitates careful monitoring of bone health and the implementation of preventive measures such as VD and calcium supplementation, lifestyle changes, and possibly pharmacological interventions to maintain bone density.

Additionally, this study demonstrated a negative correlation between serum VD levels and total number of relapses in the last two years, aligning with findings by Mowry et al. who observed that higher serum vitamin D levels in MS patients were associated with a reduced risk of clinical relapse and slower accumulation of gadolinium-enhancing lesions on MRI[28],, and Smolders et al who showed a lower rate of relapses in patients with elevated levels of VD [29]. We found no significant correlation between VD levels and EDSS while a previous study noted that all patients with an EDSS score $\geq$ 4.5 had deficient VD levels, while all patients with sufficient VD levels had an EDSS score $\leq$ 2, indicating that the relation between VD and EDSS is not linear [16]. The EDSS score of our patients was 2.8 ± 1.2. Additionally, this study found a negative correlation between disease duration and ionized serum calcium levels, consistent with previous research showing decreased Ca^{2+} concentration with longer disease duration and an increase during relapses [30]. Martyna Lis et al. also reported initially low ionized calcium levels, which further decreased following VD supplementation, likely due to the role of VD in regulating Ca^{2+} concentration in the body [31].

A negative correlation was observed between BMD, measured by the Z-score of the femur, and the disability score assessed using the EDSS. Ayatollahi et al. proposed immobility as a significant contributing factor to BMD loss [32]. According to their findings, MS patients with longer illness duration and higher EDSS scores had considerably reduced BMD, which aligns with our results. Multiple studies have reported similar findings [19, 33, 34]. Coskun et al. identified risk factors for decreased BMD in MS patients. They found that 20.9% of the 67 patients had low densitometry BMD at the femoral neck. BMD decreased with longer disease duration and significant disability with high EDSS scores [35]. On the other hand, a previous study by Zorzon et al. hadn't identified decreases in BMD at the lumbar spine or hip among patients with lower disability levels, as indicated by a mean EDSS score of less than 3 [36]. MS frequently results in reduced mobility and physical activity, which are crucial for maintaining bone density. The lack of weight-bearing activities due to MS can accelerate bone loss.

Regarding radiological data, there was a significant adverse relationship between lesion load in MRI

brain scans of MS patients and the Z-scores of the forearm, spine, and femur, which could be described by the fact that lesion load increases with the duration and progression of the disease [37]. On the other hand, there was no correlation between lesion enhancement, indicating disease activity, and DEXA scan results. Regarding black holes, there was a significant correlation with the femur Z-score. Black holes are a powerful indicator of demyelination and axonal damage, persisting for more than six months. Studies have indicated a close relationship between physical disability and their presence in imaging [38]. As far as we are aware, no prior research examined the connection that exists MS patients' bone mineral density and imaging.

In the current work, The following variables were of statistical significance predictors of low BMD: age, disease duration, number of relapses in the last two years, total number of relapses, high lesion load, and low VD levels in the univariate analysis, while only the total number of relapses in the last 2 years was independently associated with low BMD in the multivariate logistic regression analysis. While the total number of relapses in the last 2 years is recognized as a distinct risk factor for decreased BMD in patients with MS, it encompasses several contributing factors. These include reduced physical activity, increased disability, decreased sun exposure, high dose of steroid therapy and abnormal VD levels. Despite the significance of these individual factors, none act in isolation; rather, they collectively influence BMD through the cumulative effect of relapse frequency over the past two years. This is the first study that addresses the predictors of low BMD in patients with MS, highlighting the critical importance of effectively managing disease activity. As a cross-sectional study, this research has limitations in assessing changes in BMD over the progression of MS. Additionally, it lacks comparisons among different MS disease variants and the effects of various treatments on BMD, which necessitates a larger sample size of MS patients for more comprehensive analysis.

In conclusion, low BMD is frequent in MS patients with one-fifth diagnosed with osteoporosis. Vitamin D deficiency was frequently observed and related with an increased number of relapses. Patients with a higher relapserate in the past two years are at greater risk of low BMD. Early detection of low BMD is crucial for implementing preventive strategies aimed at high-risk individuals, thereby reducing their risk of fractures. To accomplish this, it is essential to educate both patients and healthcare providers about the potential for poor bone health in MS. Furthermore, targeted efforts to ensure adequate nutrition and promote physical activity will be necessary to maintain optimal bone strength along with the progression of the disease. It is worth mentioning that the UK National Institute for Health and Care Excellence (NICE) provides guidelines for osteoporotic fragility fractures [39]. NICE guidelines recommend alendronate as the first-line treatment for osteoporosis [39]. These recommendations by NICE can also be used for MS patients, as no treatment guidelines have been customized for osteoporosis in MS patients [40].

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