Vitamin D deficiency and reduced bone mineral density in multiple sclerosis: effect of ambulatory status and functional capacity

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Abstract Multiple sclerosis (MS) is a chronic disease and a major cause of disability in young adults. The aims of this study were to assess bone mass in patients with MS in comparison to healthy age- and sex-matched controls, and to evaluate factors influencing bone mineral density (BMD), and the relationship of the pain threshold at peripheral and axial sites with BMD in MS. Thirty-one patients with MS and 30 matched healthy controls participated in the study. The Kurtzke expanded disability status scale (EDSS) and the functional independence measure (FIM) were used to scale disability, mobility, and functional status. Serum 25(OH) vitamin D levels were measured. BMD was measured using dual X-ray absorptiometry (DXA). MS patients had significantly lower BMD at the lumbar spine (L2-L4) and femur trochanter compared to the matched controls. BMD of the lumbar spine was nearly 1 SD lower in MS patients compared with the healthy reference population (Z scores). MS patients had significantly lower vitamin D levels (17.3ng/ml vs 43.1ng/ml; \(P<0.001\)) compared to controls, and 19 patients (61%) had a serum level of vitamin D that was less than 20ng/ml. EDSS scores in the patients were inversely correlated with proximal femur BMD but not with spinal BMD. There was a negative correlation with the cumulative steroid dose and BMD only for femur trochanter BMD. Total myalgia scores for paravertebral muscles correlated significantly with spinal BMD. In conclusion, BMD is significantly lower in MS patients than in healthy controls, vitamin D deficiency is prevalent in MS, and ambulatory status is a determinative factor for osteoporosis in MS. Patients should be encouraged to have adequate sunlight exposure and to increase their mobility. Specific strengthening exercises for hip and back muscles in MS patients would have a substantial impact on bone density, osteoporosis, fracture risk, and mobility.

Key words Multiple sclerosis · Osteoporosis · Ambulation · Vitamin D

Introduction

Multiple sclerosis (MS) is an inflammatory autoimmune disorder of the central nervous system, manifesting as acute focal inflammatory demyelinization and axonal loss; it is one of the most important causes of neurological disability in young adults [1]. The course of the disease may be progressive or relapsing-remitting, and it may have a detrimental effect on the ambulatory status of the patient, likely leading to progressive immobilization. Intermittent or continual treatment with corticosteroids or other medications, and concomitant physiotherapy and rehabilitation interventions are the main measures used to prevent fixed disability, to provide symptomatic management of fixed neurological deficits, and, particularly, to maintain mobility [1–3]. A limited number of studies have shown that MS patients have significantly reduced bone mass and abnormal vitamin D status [2,4–6]. The major causes of reduced bone mineral density (BMD) in MS were estimated as being poor ambulatory status or immobilization; prolonged corticosteroid use; low exposure to sunlight, leading to deficiency of vitamin D; or possibly, the activation of immunoregulatory mechanisms modulating cytokine pathways that had an impact on osteogenesis [2,4–6]. Although the role of these aforementioned determinants in reducing BMD in MS has been shown, the real cause and pathogenesis of BMD reduction in MS is still uncertain.

The aims of this study were to assess: (1) bone mass in patients with MS in comparison to healthy age- and
sex-matched controls and to evaluate factors influencing BMD and (2) to determine the relationship of the pain threshold at peripheral and axial sites with BMD in the MS patients.

**Patients and methods**

Patients (n = 31; 12 men and 19 women) who were followed by the Multiple Sclerosis Outpatients Clinic and Physical Medicine and Rehabilitation Department and who had clinically definite MS [7] were enrolled. None of the patients was receiving treatment for osteoporosis or had endocrine and/or rheumatic diseases likely to affect bone metabolism. Age- and sex-matched healthy adult controls (n = 30; 10 men and 20 women) were recruited from among hospital staff or their relatives. All the women in the patient and control groups were premenopausal. Patients and controls were enrolled from June 2001 to August 2001, and all were living in Elazig (Eastern Turkey; altitude, 1067 m; latitude, 38°40’ North). All of the participants were volunteers and were informed of the nature of the study; their informed consents were obtained.

Bone mineral density was measured at the lumbar spine and proximal femur, using dual-X-ray absorptiometry (DXA), on a Lunar DPX densitometer (Lunar, Madison, W1, USA). Values for results of DXA measurements were expressed as BMD (g/cm²) and Z scores of a healthy reference population, as supplied by the manufacturer (Lunar). Short-term precision for spine and proximal femur measurements had a coefficient of variation (CV) of 1% to 2%.

Patients were all interviewed by the same physician, regarding corticosteroid usage and sunlight exposure (graded as almost none, less that 15 min/week, or longer). Cumulative steroid dosage was estimated as the sum of corticosteroids (prednisone equivalent) used, in milligrams. Patients' disability status was estimated by assigning scores on the Kurtzke expanded disability status scale (EDSS), and this was done for all participants by the same physician [8]. According to the EDSS score, patients with a score of less than 6 were considered ambulatory and those with a score of 6 or more were considered as poorly ambulatory. Patients' functional capacity was assessed by the functional independence measure (FIM) [9].

Pain threshold was measured, using a mechanical algometer, by an experienced physiatrist, from the right and left mid-pretibial region and from the right and left paravertebral regions at vertebral levels of T1-T3-T6-T9-T11-L1, and L3. Total paravertebral myalgia scores were calculated as the sum of the pain thresholds in the paravertebral regions from T1 to L3 (TMS-pv), in kilograms.

Fasting blood samples were obtained, and sera were submitted for routine biochemical analysis, including total calcium and alkaline phosphatase, and intact parathyroid hormone (iPTH), determined by chemiluminescence (Immulyte 2000; DPC, Los Angeles, CA, USA), and vitamin D metabolite 25-hydroxyvitamin D (25(OH)D; Chromysystems Instruments and Chemical, München, Germany), using high performance liquid chromatography (HPLC). Vitamin D status was categorized on the basis of previously reported data [10,11]; serum 25(OH)D concentration was defined as deficient if it was less than 10 ng/ml; as insufficient if 10 to 20 ng/ml; and as sufficient if more than 20 ng/ml.

**Statistical analysis**

Values for results are expressed as means ± SD; differences between the two groups at baseline were assessed using the t-test. Spearman rank and Pearson correlation coefficients were used to assess relationships between parameters. Multivariate linear regression analysis was used to estimate the independent effects of some variables on BMD. A two-tailed P value of less than 0.05 was considered statistically significant. The Statistics Package for Social Sciences (SPSS, Chicago, IL, USA) was used for the analyses.

**Results**

Patient and control descriptive characteristics and bone mass results are shown in Tables 1 and 2. There was no significant difference in age, height, or body mass index (BMI) between patients and controls. Patients with MS had significantly lower BMD at the lumbar spine (L2-L4) and at the femur trochanter when compared to the age- and sex-matched controls. The BMD of the lumbar spine (L2-L4) was nearly 1 SD (Z score mean, −0.98, range, 1.3 to −2.9) lower in MS patients when compared to the BMD values of a healthy reference population, supplied by the manufacturer (Lunar). Patients had significantly lower 25(OH)D levels than controls, and 15 patients (61%) had serum levels of 25(OH)D of less than 20 ng/ml, which was considered as insufficient or deficient status. Eleven patients (35%) had almost none or less than 15 min/week sun exposure. One patient had a high parathyroid hormone level (68 pg/ml), 1 had hypocalcemia (7.5 mg/dl), and 2 had high levels of alkaline phosphatase (212 and 234 U/l). The levels of 25(OH)D did not correlate significantly with serum Ca, iPTH, or patients’ FIM or EDSS scores.

EDSS scores were inversely correlated with BMD at the femur neck (r = −0.66; P < 0.0001), Ward’s (r = −0.60; P < 0.0001), and the femur trochanter (r = −0.54; P = 0.002; Fig. 1A–C). Bone mineral density at the lumbar spine (L2-L4) did not correlate with EDSS (Table 3). The levels of 25(OH)D did not have a significant correlation with BMD measurements. The cumulative steroid dose correlated only with femur trochanter BMD (r = −0.38; P = 0.03). FIM motor scores correlated with femur neck BMD (r = 0.72; P < 0.0001), Ward’s BMD (r = 0.59; P < 0.0001), and trochanter BMD (r = 0.57; P = 0.001). The total paravertebral myalgia scores correlated with L2–L4 BMD (r = 0.35; P = 0.05), but not with proximal femur BMD. The right and left mid-pretibial pain scores did not correlate with BMD measurements.