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Reduced Bone Mass and Fat-Free Mass in Women with Multiple Sclerosis: Effects of Ambulatory Status and Glucocorticoid Use

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Abstract. Multiple sclerosis (MS) is associated with reduced bone mass and vitamin D deficiency. The underlying pathophysiology of the bone disease is uncertain, however, acute and long-term glucocorticoid use, progressive immobilization, vitamin D deficiency, and possibly skeletal muscle atrophy are likely to be determinants. The aims of this study were to determine (a) whether multiple sclerosis is associated with reduced fat-free mass and (b) whether in patients with multiple sclerosis, ambulation ability or glucocorticoid use is associated with bone mass and/or fat-free mass. Seventy-one female patients with MS were compared with 71 healthy, age-matched female controls. Total body bone mineral content (TBBMC, kg), fat mass (FM, kg), and fat-free mass (FFM, kg) were measured using dual X-ray absorptiometry. Disability status was graded according to the Kurtzke Expanded Disability Status Scale (EDSS) as ambulatory, with or without aide (EDSS score of 0 to 6.5), or predominantly wheelchair bound (EDSS score > 6.5). The patients with MS, when compared to age-comparable controls, had deficits in TBBMC (≈ 8%, −0.3 ± 0.1 SD, $P < 0.04$) and FFM (≈ 5%, −0.3 ± 0.1 SD, $P < 0.01$). Both TBBMC and FFM were negatively associated with EDSS score ($r = 0.33$, $P < 0.01$, and $r = 0.41$, $P < 0.01$, respectively). Patients with MS who were nonambulatory had even greater deficits in TBBMC and FFM as compared with age-matched controls (−0.6 ± 0.1 SD, $P < 0.01$, and −0.6 ± 0.1 SD, $P < 0.01$, respectively). By contrast, as compared with age-comparable controls, ambulatory patients with MS had no deficits in bone mass or soft tissue mass. When compared with ambulatory patients with MS, nonambulatory patients with MS had deficits in TBBMC and FFM ($P < 0.01$ and $P < 0.01$, respectively). The difference in TBBMC was largely caused by the difference in fat-free mass, whereas the difference in FFM was largely caused by the difference in glucocorticoid use based on analysis of covariance. We conclude that in patients with multiple sclerosis, physical disuse is the main determinant for the reduction in bone mass. Glucocorticoid treatment is the major determinant of the reduction in fat-free mass and thus also contributes to the reduction in bone mass.

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Multiple sclerosis (MS) is a gait disorder characterized by acute episodes of neurological defect leading to progressive immobilization [1]. Management of multiple sclerosis includes intermittent or continuous treatment with corticosteroids and includes physiotherapy, particularly during the later stages, to maintain mobility. Multiple sclerosis is associated with vitamin D deficiency and reduced bone mass [2]. It is uncertain, however, whether the pathogenesis of the reduced bone mass involves vitamin D deficiency or whether both the reduced bone mass and vitamin D deficiency are secondary to the disease.

Prolonged immobilization predisposes bones to fractures since it is associated with the loss of bone and skeletal muscle [3–11]. The rate, type, and site-specificity of bone loss can be determined by the duration, severity, and site of disuse. Bone loss following weightlessness during space simulation is similar to the amount of bone loss during bed-rest [3]. Furthermore, prolonged corticosteroid use is associated with catabolism of skeletal muscle and bone loss, which predisposes bones to fractures [11–15]. Therefore, in patients with MS, both prolonged disuse and glucocorticoid use may cause an increase in bone fragility and may reduce skeletal muscle mass; both of these results increase fracture risk.

The aims of this study were to determine (a) whether multiple sclerosis is associated with reduced fat-free mass and (b) whether, in patients with multiple sclerosis, ambulation ability or glucocorticoid use is associated with bone mass and/or fat-free mass.

Subjects and Methods

Seventy one female patients with MS were compared to 71 healthy, age-comparable female controls (45.6 ± 1.1 vs. 47.7 ± 1.2 years, P = NS). Both groups were composed of white females only. For the control group, subjects with atraumatic fractures or any secondary causes of osteoporosis, such as corticosteroid use, hyperparathyroidism, and hyperthyroidism, or use of any medication known to affect bone metabolism, were excluded from the study. The patients with MS were recruited from the Helen Hayes Hospital, Multiple Sclerosis Center, while the age-comparable

controls were selected from a cohort of healthy subjects recruited by the Regional Bone Center for the establishment of a reference range. The study was approved by the Institutional Review Board of Helen Hayes Hospital and all patients provided informed consent.

Patients with MS were divided into two groups: ambulatory and nonambulatory, based on the Kurtzke Expanded Disability Status Score (EDSS) [29]. For purposes of the study, patients were characterized as ambulatory if their EDSS score was 0 to 6.5 and nonambulatory if their EDSS score was greater than 6.5. All patients with MS received pulsed pharmacological and supraphysiological doses of glucocorticoids according to the following protocol: one steroid month was composed of Solumedrol that was administered intravenously at 1.0 g for 1 week, then 0.5 g for 3 days, and 0.25 g for another 3 days, followed by oral Prednisone at 80 mg for 1 week, 60 mg for 1 week, 40 mg for 4 days, 20 mg for 4 days, 10 mg for 4 days, and 5 mg for 4 days. Glucocorticoid use was therefore expressed as duration of use (months) and was determined from a interviewer-administered questionnaire. We have previously reported that the mean 25(OH)D levels in this group of patients with MS were in the insufficient range, and 12 patients (23%) had frank vitamin D deficiency [2]. The vitamin D status in both the ambulatory and nonambulatory MS patients did not differ between the groups. Likewise, ionized calcium was within the normal range and did not differ between ambulatory and nonambulatory patients with MS.

Measurement of Bone Mass and Body Composition

Total body bone mineral content (TBBMC), total body fat-free mass (FFM), and total body fat mass (FM) was measured in the patients with MS using dual X-ray absorptiometry (Norland XR-26, Fort Atkinson, WI). For the control group, total body bone mass and body composition was measured using dual X-ray absorptiometry (Norland XR-26, Fort Atkinson, WI, in 41 subjects and Lunar DPX-L, Madison, WI, in 30 subjects). The results for the 30 control subjects measured on the Lunar densitometer were adjusted to Norland equivalent values using linear regression analysis based on 78 healthy female subjects. The conversion equations are shown below:

$$\mathrm{TBBMC_{XR}\ (g)} = 1.103(\mathrm{TBBMC_{DPX\text{-}L}}) + 79.01527;\quad r = 0.90,\ P < 0.01$$

$$\mathrm{Fat_{XR}\ (\%)} = 1.032\ (\%\mathrm{Fat_{DPX\text{-}L}}) + 9.23;\quad r = 0.95,\ P < 0.01$$

$$\mathrm{FM_{XR}\ (g)} = 1.156\ (\mathrm{FM_{DPX\text{-}L}}) + 2334.6;\quad r = 0.98,\ P < 0.01$$

$$\mathrm{FFM_{XR}\ (g)} = 0.7152\ (\mathrm{FFM_{DPX\text{-}L}}) + 2908;\quad r = 0.83,\ P < 0.01$$

Statistical Analysis

Comparisons between MS patients and age-comparable controls were done using unpaired t tests. Linear regression analysis was used to determine the relationship between total body bone mineral content and fat-free mass with EDSS score. Comparisons of nonambulatory patients with MS, ambulatory patients with MS, and age-comparable controls were performed using analysis of variance with Tukey HSD post-hoc tests. The effect of covariates on the difference between ambulatory and nonambulatory patients with MS was determined using analysis of covariance. Bone mass and fat-free mass were expressed in absolute terms (kg) and as Z-scores (SD). Z-scores were calculated as the difference between the observed and predicted value (based on the fitted equations adjusting for the covariates, age, and menopausal status in the control group), divided by the square root of the estimated variance for the control group. All analyses were performed using Systat for Windows.

Results

Mean descriptive characteristics and indices of body composition and bone mass are shown in Table 1. In the patients with MS, 10 had sustained fractures (4 ankle, 2 vertebral, 1 hip, 1 rib, 1 Colle's, and 1 leg). There were no significant differences in age, height, or weight between the controls and the patients with MS. However, compared to age-comparable controls, BMI in patients with MS was statistically less than the BMI of controls (23.6 ± 0.6 vs. 26.0 ± 1.0 kg/m^2, $P < 0.05$). Compared to age-matched controls, patients with MS as a whole group had deficits in TBBMC and FFM when expressed as Z-scores (both −0.3 ± 0.1 SD, $P < 0.04$), but not when expressed in absolute terms. After adjustment for the deficit in FFM, TBBMC was no longer significantly different in patients with MS as compared with age-comparable controls. As shown in Figure 1, EDSS score was negatively associated with both TBBMC ($r = -0.33$, $P < 0.01$) and FFM ($r = -0.41$, $P < 0.01$). Total body bone mineral content was marginally associated with FFM ($r = 0.23$, $P = 0.06$), however, after adjustment for FFM, EDSS score was an independent determinant of TBBMC, and FFM failed to reach statistical significance ($P = 0.4$).

As shown in Table 1 and Figure 2, patients with MS who were nonambulatory, had greater deficits in TBBMC as compared with age-matched controls, when expressed both in absolute terms (2.3 ± 0.1 vs. 2.5 ± 0.1 kg, $P < 0.05$) and as a standardized score (−0.6 ± 0.1 SD, $P < 0.01$). Also, when compared to ambulatory MS patients, nonambulatory MS patients had a deficit in TBBMC whether expressed in absolute terms (2.3 ± 0.1 vs. 2.6 ± 0.1 kg, $P < 0.05$) or as a standardized score (−0.6 ± 0.1 vs. 0.0 ± 0.2, $P < 0.01$). Fat-free mass in nonambulatory MS patients was significantly reduced as compared with age-matched controls when expressed in absolute terms (26.8 ± 0.7 vs. 29.8 ± 0.6 kg, $P < 0.01$) or as a standardized score (−0.6 ± 0.1 SD, $P < 0.01$). When compared with ambulatory MS patients, nonambulatory MS patients had a deficit in FFM when expressed in absolute terms (26.8 ± 0.7 vs. 29.8 ± 0.7 kg, $P < 0.02$) and as a standardized score (−0.6 ± 0.1 vs. 0.0 ± 0.2 SD, $P < 0.01$). Ambulatory patients with MS were similar to age-matched controls for all measurements (P = NS for all, Table 1).

Comparing ambulatory MS patients to nonambulatory MS patients, the duration of corticosteroid use (months) failed to reach statistical significance (3.2 ± 0.8 vs. 5.4 ± 0.8 months, $P = 0.06$), however, the duration of corticosteroid use was considered to be biologically significant and was treated as a possible covariate. In ambulatory MS patients, 9 women were postmenopausal as compared with 11 postmenopausal nonambulatory MS patients. Years since menopause did not differ between the two groups. Following the results of the analysis of covariance, the difference in FFM between ambulatory and nonambulatory patients with MS was accounted for by the duration of glucocorticoid use (adjusted means: 29.1 ± 0.8 vs. 27.0 ± 0.8 kg, P = NS), whereas the difference in TBBMC between ambulatory and nonambulatory patients with MS was accounted for by the difference in FFM (adjusted means: 2.5 ± 0.1 vs. 2.3 ± 0.1 kg, P = NS).

Discussion

These data suggest that nonambulatory patients with MS

Table 1. Age, height, weight, glucocorticoid use, bone mass, fat mass, and fat-free mass in age-comparable controls and women with multiple sclerosis

	Controls (71)	MS Patients		
		Total (71)	Ambulatory (39)	Nonambulatory (32)
Age (years)	47.7 ± 1.2	45.6 ± 1.1	44.8 ± 1.6	46.5 ± 1.8
Height (cm)	161.0 ± 1.2	163.5 ± 0.8	164.7 ± 1.1	162.0 ± 1.3
Weight (kg)	66.3 ± 1.6	63.0 ± 1.7	65.2 ± 2.2	60.3 ± 2.4
BMI (kg/m)	26.0 ± 1.0	23.6 ± 0.6[a]	24.1 ± 0.9	23.0 ± 0.8
EDSS score			5.8 ± 0.2	7.8 ± 0.2[b]
Steroid use (months)			3.2 ± 0.8	5.4 ± 0.8[c]
Disease duration (years)			8.5 ± 1.2	11.6 ± 1.3
TB BMC (kg)	2.5 ± 0.1	2.4 ± 0.1	2.6 ± 0.1	2.3 ± 0.1[a,d]
Z-score		−0.3 ± 0.1[c]	0.0 ± 0.2	−0.6 ± 0.1[b,f]
Fat mass (%)	47.8 ± 1.2	48.0 ± 1.2	47.6 ± 1.7	48.6 ± 1.9
Z-score		0.1 ± 0.2	−0.1 ± 0.2	0.0 ± 0.2
Fat mass (kg)	31.8 ± 1.6	30.4 ± 1.5	31.2 ± 2.0	29.4 ± 2.1
Z-score		−0.1 ± 0.1	−0.1 ± 0.2	−0.2 ± 0.2
Fat-free mass (kg)	29.8 ± 0.6	28.5 ± 0.5	29.8 ± 0.7	26.8 ± 0.7[f,g]
Z-score		−0.3 ± 0.1[c]	0.0 ± 0.2	−0.6 ± 0.1[b,f]
TB BMC:FFM (%)	8.2 ± 0.2	8.0 ± 0.2	8.0 ± 0.3	7.9 ± 0.4
Z-score		−0.2 ± 0.1	−0.2 ± 0.2	−0.2 ± 0.2

[a] $P < 0.05$ compared to controls
[b] $P < 0.01$ compared to ambulatory patients with MS
[c] $P = 0.06$ compared to ambulatory patients with MS
[d] $P < 0.05$ compared to ambulatory patients with MS
[e] $P < 0.04$ compared to controls
[f] $P < 0.01$ compared to controls
[g] $P < 0.02$ compared to ambulatory patients with MS

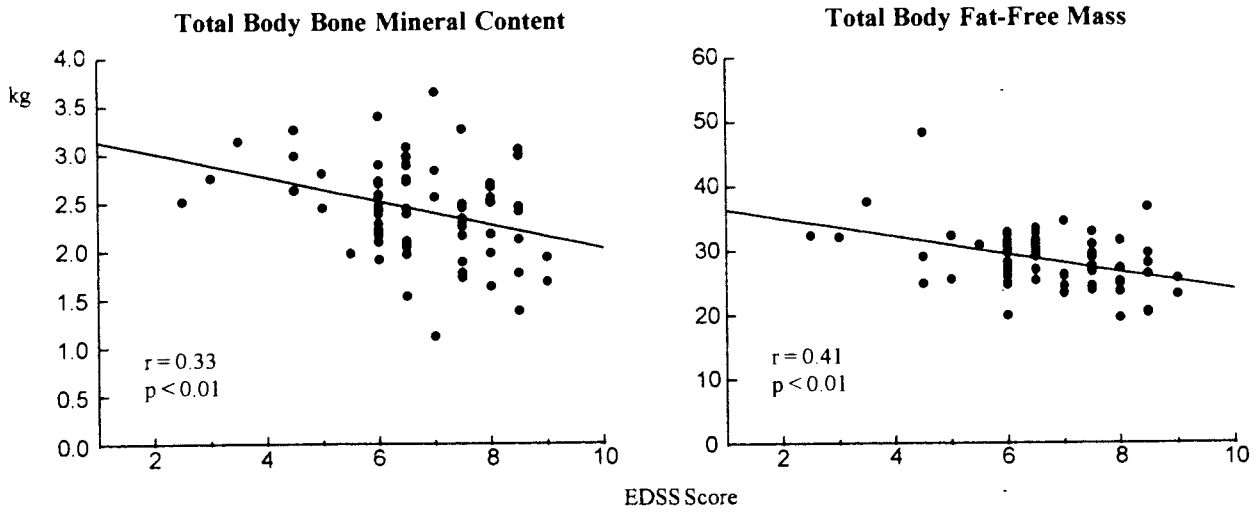

Fig. 1. Total body bone mineral content and fat-free mass as a function of disability status in patients with multiple sclerosis.

may be at increased risk of fracture caused by a reduction in bone mass and lean body mass. The severity of the deficit in bone mass was related to the degree of physical disuse. By contrast, ambulatory patients with MS had no difference in bone mass or body composition as compared with age-comparable controls, suggesting that either the time since diagnosis or the disease process may be different. In addition, glucocorticoid use had minimal effects on bone mass and fat-free mass in mobile patients. In nonambulatory patients with MS, immobility and corticosteroid use, possibly reflecting a more severe disease condition, accentuated the deficit in bone mass.

Prolonged immobility in clinical cases such as spinal injury and stroke has been shown to lead to osteoporosis [3–8]. Generalized immobilization, such as with quadriplegia, leads to generalized osteoporosis, whereas hemiplegia causes osteoporosis in the affected limb. Nonambulatory patients with MS have generalized immobility and, in this study, total body bone mineral content was reduced by 8% as compared with ambulatory patients with MS, and by

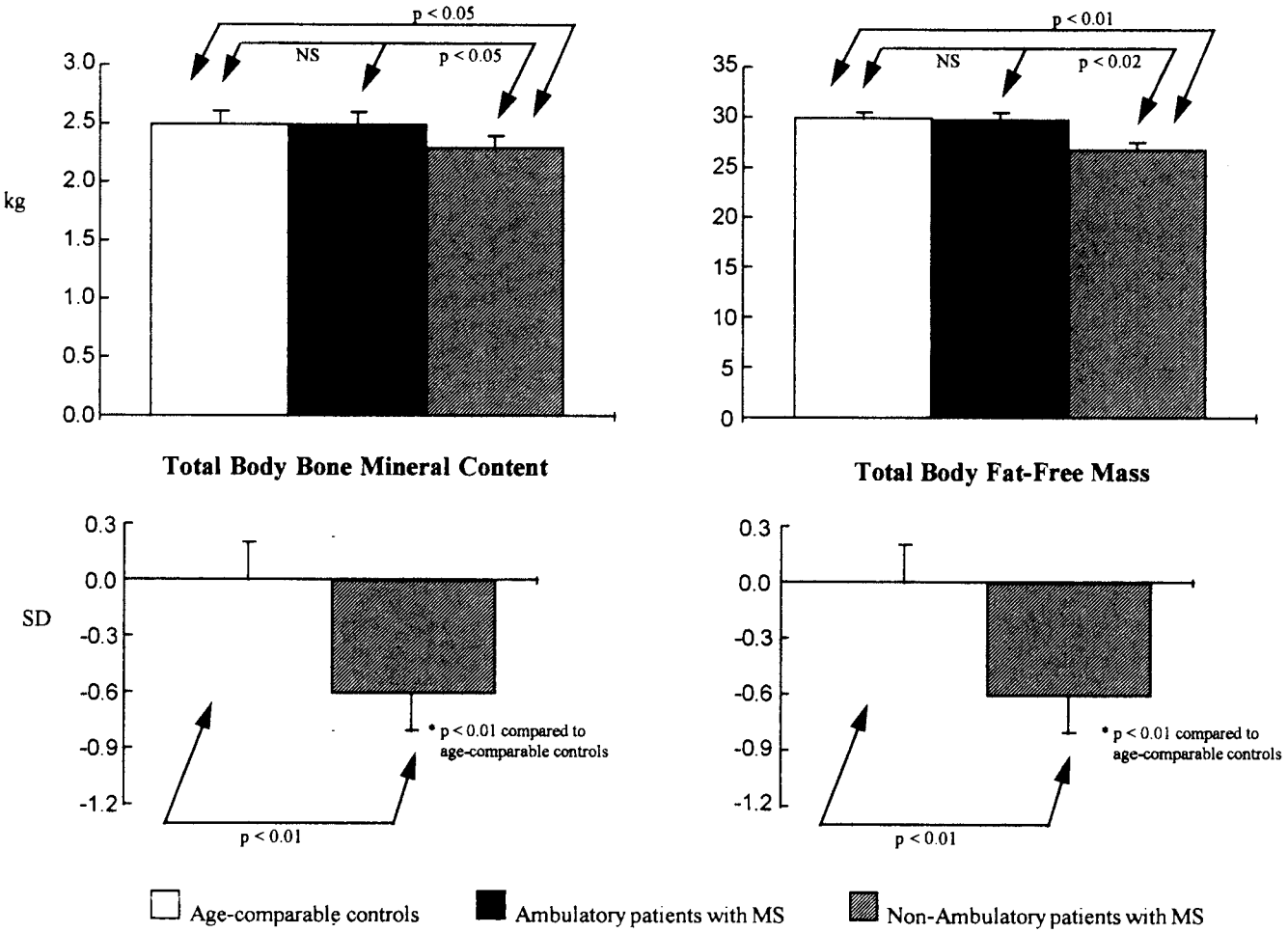

Fig. 2. Total body bone mineral content and fat-free mass in age-comparable controls, ambulatory patients with multiple sclerosis, and nonambulatory patients with multiple sclerosis, expressed in absolute terms (kg) and as a Z-score (SD).

11.5% as compared with age-comparable controls. It is uncertain whether this reduced bone mass is reversible. The bone loss associated with physical disuse is possibly caused by an increase in bone turnover or as a result of altered bone cell function, which may make the bone loss irreversible. Increased urinary calcium excretion has been demonstrated in metabolic studies, suggesting an increased bone turnover state [3–4, 9, 16]. Whereas the mechanisms may be unclear, these observations highlight the importance of mechanical usage in patients with MS and highlight the need to implement appropriate loading in the management of these patients.

Skeletal muscle depletion is a consequence of physical disuse and glucocorticoid usage [11, 17–24]. Nonambulatory patients with MS had reduced fat-free mass (≈10%) as compared to ambulatory patients with MS and age-comparable controls. Whereas both physical disuse and glucocorticoid use in this group of patients would largely account for the deficit in fat-free mass, it would appear, based on the analysis of covariance, that the duration of glucocorticoid use is the main determinant for this deficit. Prolonged use of glucocorticoids causes catabolism of skeletal muscle [11, 19–24]. Decreased amino acid transport into muscle and increased glutamine synthesis activity with resultant muscle atrophy are some of the concomitant effects of glucocorticoid use on skeletal muscle.

Endogenous glucocorticoid excess also produces generalized osteoporosis, most prevalent in trabecular-rich skeletal regions [13, 15, 25–28]. The osteoporosis is most likely multifactorial, because of increased renal calcium losses, decreased gastrointestinal calcium absorption, secondary hyperparathyroidism, and increased bone turnover with depression of bone formation. Resorption cavities of greater depth may occur and may result in more rapid bone loss and possibly trabecular perforation. In both ambulatory and nonambulatory patients with MS, glucocorticoid use was not associated with total body bone mass. However, our group has previously reported that bone mass at the lumbar spine, proximal femur, and total body was higher in patients with previous steroid use [2]. This was due, at least in part, to the fact that glucocorticoid treatment is generally administered to younger patients. Furthermore, the beneficial effects of pulsed steroids on mobility in patients with MS may offset the deleterious pharmacological effects on bone and skeletal muscle. Obtaining an accurate history of glucocorticoid use from questionnaire data is inherently difficult, therefore we need to confirm these hypotheses with longitudinal data.

Deficits in bone mass and fat-free mass were associated with the severity of multiple sclerosis. Using mobility as one means of defining disease severity, we showed that ambulatory patients with MS were no different than age-

comparable controls. By contrast, nonambulatory patients with MS had a deficit in bone mass that would increase fracture risk approximately two-fold. This risk of fracture may be further increased because of the increased risk of falls associated with deteriorating visual and motor performance in patients with MS.

In summary, nonambulatory patients with MS have generalized deficits in bone mass and fat-free mass, increasing the risk of falls and fractures. Glucocorticoid catabolism of skeletal muscle largely accounted for the deficit in fat-free mass, and the deficit in fat-free mass largely accounted for the deficit in bone mass. In conclusion, in patients with MS, immobilization and glucocorticoid use are the main determinants for the decrease in fat-free mass and the increased risk of fracture and morbidity.

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References

1. Scheinberg LC, Smith CR (1987) Signs and symptoms of multiple sclerosis. In: Scheinberg LC, Holland NJ (eds) Multiple sclerosis, 2nd ed, Raven Press, New York, pp 43–51
2. Nieves J, Cosman F, Herbert J, Shen V, Lindsay R (1994) High prevalence of vitamin D deficiency and reduced bone mass in multiple sclerosis. Neurology 44:1687–1692
3. Parfitt AM (1981) Bone effects of space flight: analysis by quantum concept of bone remodeling. Acta Astronautica 8: 1083–1090
4. Schneider VS, McDonald J (1984) Skeletal calcium homeostasis and countermeasures to prevent disuse osteoporosis. Calcif Tissue Int 36:S151–S154
5. Cundy T, Grey A (1994) Mechanisms of cortical bone loss from the metacarpal following digital amputation. Calcif Tissue Int 55:164–168
6. Saltzstein RJ, Hardin S, Hastings J (1992) Osteoporosis in spinal cord injury: using an index of mobility and its relationship to bone density. J Am Paraplegia Soc 15:232–234
7. Garland DE, Stewart CA, Adkins RH, Rosen C, Liotta FJ, Weinstein DA (1992) Osteoporosis after spinal cord injury. J Orthop Res 10:371–378
8. Elias AN, Gwinup G (1992) Immobilization osteoporosis in paraplegia. J Am Paraplegia Soc 15:163–170
9. Whedon GD (1984) Disuse osteoporosis: physiological aspects. Calcif Tissue Int 36:S146–S150
10. Manaire P, Meunier P, Edouard C, Bernard J, Courpron P, Bourret J (1974) Quantitative histological data on disuse osteoporosis: comparison with biological data. Calcif Tissue Res 17:57–73
11. Marone JR, Falduto MT, Essig DA, Hickson RC (1994) Effects of glucocorticoids and endurance training on cytochrome oxidase expression in skeletal muscle. J Appl Physiol 77: 1685–1690
12. Hahn TJ (1978) Corticosteroid-induced osteopenia. Arch Intern Med 138:882–885
13. Hahn TJ, Boisseau WV, Avioli LV (1974) Effect of chronic corticosteroid administration on diaphyseal and metaphyseal bone mass. J Clin Endocrinol Metab 39:274–281
14. Adinoff AD, Hollister JR (1983) Steroid-induced fractures and bone loss in patients with asthma. N Engl J Med 309: 265–268
15. Reid IR (1994) Steroid osteoporosis. Spine State Art Rev 8: 91–110
16. Evans RA, Bridgeman M, Hills E, Dunstan CR (1984) Immobilization hypercalcemia. Miner Electrolyte Metab 10:244–248
17. Dodd SL, Powers SK, Vrabas IS, Eason JM (1995) Interaction of glucocorticoids and activity patterns affect muscle function. Muscle Nerve 18:190–195
18. Tirapegui JO, Yahya ZA, Bates PC, Millward DJ (1994) Dietary energy, glucocorticoids and the regulation of long bone and muscle growth in the rat. Clin Sci 87:599–606
19. Louard RJ, Bhushan R, Gelfand RA, Barrett EJ, Sherwin RS (1994) Glucocorticoids antagonize insulin's antiproteolytic action on skeletal muscle in humans. J Clin Endocrinol Metab 79:278–284
20. Fimbel S, Abdelmalki A, Mayet MH, Sempore B, Koubi H, Pugeat M, Dechaud H, Favier RJ (1993) Exercise training fails to prevent glucocorticoid-induced muscle alterations in young growing rats. Pflugers Arch 424:369–376
21. Chromiak JA, Vandenburgh HH (1992) Glucocorticoid-induced skeletal muscle atrophy in vitro is attenuated by mechanical stimulation. Am J Physiol 262:C1471–C1477
22. Falduto MT, Young AP, Hichson RC (1992) Exercise interrupts ongoing glucocorticoid-induced muscle atrophy and glutamine synthetase induction. Am J Physiol 263:E1157–E1163
23. Chong PK, Jung RT, Scrimgeour CM, Rennie MJ (1994) The effect of pharmacological dosages of glucocorticoids on free living total energy expenditure in man. Clin Endocrinol 40: 577–581
24. Lobo MJ, Remesar X, Alemany M (1993) Effect of chronic intravenous injection of steroid hormones on body weight and composition of female rats. Biochem Mol Biol Int 29:349–358
25. Finkelstein JS, Cleary RL, Butler JP, Antonelli R, Mitlak BH, Deraska DJ, Zamora-Quezada JC, Neer R (1994) A comparison of lateral versus anterior-posterior spine dual energy x-ray absorptiometry for the diagnosis of osteopenia. J Clin Endocrinol Metab 78:724–730
26. Russekk RG (1993) Cellular regulatory mechanisms that may underlie the effects of corticosteroids on bone. Br J Rheumatol 32:S6–S10
27. Lyles KW, Jackson TW, Nesbitt T, Quarles LD (1993) Salmon calcitonin reduces vertebral bone loss on glucocorticoid-treated beagles. Am J Physiol 264:E938–E942
28. Lukert BP (1992) Glucocorticoid-induced osteoporosis. South Med J 85:2S48–2S51
29. Kelly R (1985) Clinical aspects of multiple sclerosis. In: Koetsier JC (ed) Handbook of clinical neurology, Elsevier Science, New York, pp 49–78