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Statistical, pathophysiological and clinical aspects of the relationship between multiple sclerosis and osteoporosis

Statystyczne, patofizjologiczne i kliniczne aspekty związku między stwardnieniem rozsianym i osteoporozą

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Abstract

Recently there has been a large increase in a number of publications regarding bone health in multiple sclerosis as well as studies exploring the possible role of vitamin D in the aetiology of the condition. However, the relationship between multiple sclerosis and osteoporosis remains not widely discussed among clinicians. The aim of our review article is to present crucial aspects of such relationship as well as therapeutic options. There are many statistical facts suggesting that correlation between two said diseases occurs. The prevalence of osteoporosis clinical features, like pathological fractures, decreased bone mineral density or low vitamin D serum level, is greater in patients with multiple sclerosis. These facts can be explained by a wide variety of areas and pathways which are common for multiple sclerosis and osteoporosis. The functions of different mediators involved in the pathophysiology of diseases, the role of vitamin D and the adverse effects of drugs administered in multiple sclerosis serve as the best examples. Unfortunately, no uniform guidelines on the management of multiple sclerosis patients with osteoporosis have been established so far. However, the guidelines of the United Kingdom National Institute for Health and Care Excellence and National Osteoporosis Society are recommended in such cases. The most important are an appropriate vitamin D and calcium supplementation, smoking cessation, alcohol intake reduction and more of physical activity. There is a strong need to spread this knowledge among clinicians. A better understanding of the topic might result in the creation of diagnostic and therapeutic guidelines with this respect.

Key words: multiple sclerosis, osteoporosis, bone health, fractures, vitamin D

Streszczenie

W ostatnim czasie znacznie wzrosła liczba publikacji dotyczących stanu zdrowia kości w stwardnieniu rozsianym, jak również możliwej roli witaminy D w etiologii wspomnianej jednostki chorobowej. Jednakże związek między stwardnieniem rozsianym i osteoporozą w dalszym ciągu nie jest szeroko omawiany wśród klinicystów. Celem naszego artykułu poglądowego jest przedstawienie kluczowych aspektów wspomnianej korelacji oraz opcji terapeutycznych. Wiele faktów z zakresu statystyki przemawia za tym, że związek między omawianymi dwoma chorobami występuje. Rozpowszechnienie cech charakterystycznych dla obrazu klinicznego osteoporozy, takich jak złamania patologiczne, zmniejszenie mineralnej gęstości kości oraz niskie stężenie witaminy D w surowicy, jest większe wśród chorych na stwardnienie rozsiane. Może to być wyjaśnione licznymi, wspólnymi dla stwardnienia rozsianego i osteoporozy, obszarami i ścieżkami patofizjologicznymi. Ich przykładem są funkcje różnych mediatorów odgrywających rolę w patogenezie obu chorób, rola witaminy D oraz działania niepożądane leków stosowanych w terapii stwardnienia rozsianego. Niestety, do tej pory nie powstały uniwersalne wytyczne dotyczące postępowania w sytuacji współwystępowania stwardnienia rozsianego i osteoporozy. W takich przypadkach rekomendowane są wytyczne Narodowego Instytutu Zdrowia i Klinicznej Doskonałości Zjednoczonego Królestwa oraz Narodowego Towarzystwa Osteoporozy. Największe znaczenie mają odpowiednia suplementacja witaminy D i wapnia, zaprzestanie palenia, zmniejszenie spożycia alkoholu i zwiększenie aktywności fizycznej. Istnieje silna potrzeba rozpowszechnienia znajomości tego zagadnienia wśród klinicystów. Lepsze jego rozumienie może doprowadzić do stworzenia wytycznych uwzględniających aspekty diagnostyczne i terapeutyczne.

Słowa kluczowe: stwardnienie rozsiane, osteoporoza, zdrowie kości, złamania, witamina D

INTRODUCTION

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) associated with the processes of inflammation and demyelination which remains not fully understood. Initially, the inflammation is usually transient and remyelination occurs, but over time the pathological changes become dominated by a widespread microglial activation connected with an extensive and chronic neurodegeneration. Multiple sclerosis is the main cause of non-traumatic neurological disability affecting young European adults and their descendants (Hollenbach and Oksenberg, 2015).

Osteoporosis is a common metabolic bone disease based on a decreased mineral density and microarchitectural disturbances of the bone tissue. The imbalance between bone resorption and formation is a crucial pathophysiological factor in osteoporosis. It leads to an increased risk of fracture, which results in large-scale morbidity particularly among postmenopausal women (Wolski *et al.*, 2015).

Therefore, both multiple sclerosis and osteoporosis are significant and still growing social problems. What is more, the relationship between them has been noticed. As a result, there has been an increasing publication rate regarding bone health in MS in the last 10 years, as well as a large number of studies exploring the possible role of vitamin D in the aetiology of the condition. However, this topic is still not widely known and discussed among clinicians.

The aim of this review article is to present crucial aspects of the relationship between MS and osteoporosis as well as therapeutic options. A better understanding of the topic might result in the establishment of diagnostic and therapeutic guidelines and will definitely increase the alertness of clinicians, which highlights its scientific and clinical significance.

CLINICALLY RELEVANT STATISTICAL DATA

The relationship between MS and osteoporosis seems to have a strong influence on statistical facts connected with these diseases.

First of all, many authors have noticed that the prevalence of fractures in patients with MS is greater than in control groups and proved such correlation. According to the study conducted by North American Research Committee on Multiple Sclerosis (NARCOMS), 15% of subjects suffering from MS had a history of fracture after the age of 13. Among those reporting fractures, 46.2% reported multiple fractures (Marrie *et al.*, 2009). In a case-control study performed in 1998, authors documented a self-reported fracture rate in the absence of major trauma occurring above the age of 35 years in 22% of 54 patients with MS with a mean Expanded Disability Status Scale (EDSS) result of 6.2 compared to only 2% of 49 healthy controls (Cosman *et al.*, 1998).

Secondly, the structure of the bone tissue is changed in MS patients, which can be easily assessed using bone mineral density (BMD) and total body bone mineral (TBBM) content parameters. In 2010, Hearn and Silber conducted a cumulative meta-analysis in which they compared several studies assessing BMD or TBBM in healthy controls and in MS patients. The meta-analysis undoubtedly shows that MS is associated with lower values of BMD as well as TBBM (Hearn and Silber, 2010). In addition, the study performed by Weinstock-Guttman *et al.* (2004) showed that 80% of male MS patients were osteopenic or osteoporotic. These findings can explain more frequent fractures in MS patients compared to the general population.

Furthermore, the level of vitamin D is often investigated in MS patients. Vitamin D plays a key role in bone structure and calcium level maintenance. Its deficit is an essential osteoporosis risk factor while its adequate intake can delay or prevent osteoporosis (Ishimi, 2015). Polachini *et al.* (2016) have recently indicated significantly decreased serum levels of vitamin D in MS patients in relation to healthy individuals. According to the review article by Gibson and Summers (2011), serum 25-hydroxyvitamin D (25-OHD) insufficiency or deficiency in people with MS ranges from 17% to 86.7%, but five of the nine case-control studies have found no statistically significant difference in the serum 25-OHD levels between people with MS and healthy controls. Although these results are not consistent, they allow to assume that MS patients might be at high risk of osteoporosis.

Lastly, many authors have been mentioning the correlation between MS or its relapses occurrence and the latitude of the place of residence. According to Niino *et al.* (2014), MS shows a multifold increase in the prevalence with an increase in latitudes, both north and south of the equator. One of the potential factors related to the difference of the prevalence might be vitamin D, because the strength of ambient ultraviolet light which is essential for vitamin D production decreases as latitude increases. However, the relationship between MS, the latitude of residence, vitamin D and osteoporosis remains unclear.

MULTIPLE SCLEROSIS AND OSTEOPOROSIS – COMMON AREAS AND PATHWAYS

In this paragraph, we attempt to present the most significant reasons for statistical facts mentioned in the previous one as well as to show correlations between them. Generally, there are many common areas in the field of pathophysiology, risk factors and treatment of MS and osteoporosis. Certainly, it contributes to the relationship mentioned in our article.

Cytokines and other mediators

Humoral mediators play a key role in the pathogenesis of either MS or osteoporosis. For instance, proinflammatory cytokines like interleukin (IL) 1, tumour necrosis factor

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(TNF)-α, IL-6, and IL-11 are known to be released from T helper (Th) as well as other cells and being an important factor contributing to immunological disturbances in MS (Gupta *et al.*, 2014). On the other hand, these cytokines have been shown to promote osteoclastogenesis. It is essential in the osteoporosis pathogenesis due to the effect on bone loss (via the expression of nuclear factor κB ligand – RANKL) (McLean, 2009).

Moreover, levels of osteopontin were found to be increased in the cerebrospinal fluid of MS patients and shown to be positively correlated with bone density of the femur neck (Gupta *et al.*, 2014). These findings suggest that osteopontin is involved in a pathway common to the development of both MS and osteoporosis.

Furthermore, there are many neuronal factors released from CNS cells which, according to a number of studies, might play a role in the pathogenesis of both MS and osteoporosis. Examples of such neuromediators are leptin, neuromedin U and neuropeptide Y. Because of contrary and often controversial conclusions of different studies, their detailed role in MS and osteoporosis still remains undiscovered.

Vitamin D

The relationship between MS, osteoporosis and vitamin D is sophisticated and controversial. The role of vitamin D in MS has been investigated both from the point of view of bone health and to explore a possible link to the aetiology of the condition and the occurrence of relapses of MS.

Surprisingly, there seems to be no correlation between vitamin D levels and BMD in MS. In 2012, Triantafyllou *et al.* documented the lack of correlation between vitamin D levels and decreased BMD at the femoral neck and the lumbar spine in the relapsing-remitting MS patients and stated that vitamin D insufficiency appeared not to be the underlying cause of secondary osteoporosis in MS. In 2004, a study was carried out which showed that only 37.5% of MS patients with low BMD had decreased vitamin D serum levels (Weinstock-Guttman *et al.*, 2004). The reason for such astonishing findings may be explained by vitamin D receptor gene polymorphisms. According to the study performed by Lambrinoudaki *et al.* (2013), vitamin D receptor's Bsm1 polymorphism is associated with a mild effect on BMD in younger patients with MS. However, larger studies are necessary to corroborate these findings.

As mentioned above, the correlation between vitamin D levels and MS can also be investigated in the aspect of vitamin D influence on the pathogenesis of MS, disability status as well as the occurrence of relapses in MS patients. One Australian case-control study found a strong negative correlation between the degree of disability, measured by EDSS, and serum 25-OHD levels (van der Mei *et al.*, 2007). In addition, it has been indicated that there is an association between a low vitamin D status at the start of the relapsing-remitting MS and the early conversion to secondary progressive MS (Muris *et al.*, 2015). These results suggest that vitamin D has a protective effect against pathogenic factors in MS. Many authors have been trying to explain these relations. Findings of the study conducted by Gu *et al.* (2015) conclude that lesion-associated apoptotic signals in the CNS are reduced following the administration of vitamin D. The results of a study conducted in 2000 suggest that CD8 lymphocytes may be a major site of 1,25-dihydroxyvitamin D_3 action, while B lymphocytes might not directly be regulated by 1, 25-dihydroxyvitamin D_3 (Veldman *et al.*, 2000). These conclusions highlight an important role of vitamin D in neuroimmunology.

Drugs

Glucocorticosteroids (GCS)

Glucocorticosteroids are basic and the most important drugs used in the treatment of relapses of MS due to their anti-inflammatory effect. On the other hand, adverse reactions of GCS connected with the bone tissue and the tendency to develop osteoporosis are well known. Methylprednisolone administered intravenously profoundly suppresses bone formation and increases bone resorption (Gibson and Summers, 2011). In fact, the results of studies are quite astonishing. According to them, fractures in MS patients are rather caused by other factors than a steroid therapy, like for example impaired gait. The study by Zorzon *et al.* (2005) showed that repeated pulses of methylprednisolone do not result in a substantially increased risk of osteoporosis in MS patients. In the meta-analysis conducted by Gibson and Summers (2011), in patient exposed to pulsed steroids over an average period of approximately 11 years, there is no significant correlation between cumulative steroid dose and the lumbar spine, the femoral neck or total body BMD. It seems likely that intermittent corticosteroid administration has a lesser effect on bones than a continuous therapy. Nonetheless, clinical alertness is necessary because harmful effects of steroid therapy on bone health in MS patients have also been documented (Dovio *et al.*, 2004).

Disease-modifying drugs

These drugs are used to slow the progression of the disease. Among them interferons are the most widely used. Unfortunately, the results and conclusions of studies investigating their potential role in osteoclastogenesis are contradictory.

There is still not enough data on the relation between glatiramer acetate and the risk of osteoporosis to make scientific conclusions.

Interestingly, several studies on the fingolimod (sphingosine-1-phosphate) influence on BMD have been performed. In 2009, Ishii *et al.* published an article in "Nature" journal in which they stated that sphingosine-1-phosphate controlled the migratory behaviour of osteoclast precursors, dynamically regulating bone mineral homeostasis in mice.

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Anticonvulsants

Patients with MS have a threefold increase in the risk to develop epilepsy. Anti-epileptic drugs are known to be harmful for bone health. As a result, chronic anticonvulsant treatment reduces bone strength and increases the risk to develop osteoporosis in MS patients.

Other factors affecting bone health in MS

Cognitive impairment occurs in 40–70% of patients with MS (Guenter *et al.*, 2015). In 2012, Batista *et al.* conducted a retrospective study in which they documented the association between a reduced BMD in patients suffering from MS and the cognitive deficit. An explanation of this result can be found in an increasing number of studies suggesting that neuronal signalling is intimately involved in bone homeostasis, mainly through the leptin-dependent central control of bone formation via the sympathetic system (Batista *et al.*, 2012).

Furthermore, falls are common in persons with MS and are related to physical disability and reduce the quality of life. As stated previously, the prevalence of epilepsy in MS patients is greater than in healthy controls. Epilepsy is also a significant risk factor of falls and fractures. These facts explain a high frequency of fractures in MS patients.

Interestingly, smoking is considered to be a major preventable risk factor of multiple sclerosis and significant (included in Fracture Risk Assessment Tool) risk factor of osteoporosis. It has been indicated that continued smoking is associated with an acceleration in time to secondary progressive MS and that those who quit fare better (Ramanujam *et al.*, 2015).

OSTEOPOROSIS TREATMENT OPTIONS IN MULTIPLE SCLEROSIS

As mentioned in the second paragraph, osteoporosis and fractures definitely worsen the quality of life and are a major cause of morbidity in patients suffering from MS. Unfortunately, no uniform guidelines on such topic have been set so far (Gupta *et al.*, 2014). Therefore, clinicians have to treat patients according to general guidelines on osteoporosis therapy, individual publications as well as their own clinical experience. Drawing any firm conclusions from single studies is very difficult due to the fact that these typically include relatively small numbers of participants, have a variety of selection criteria, and involve a range of analyses.

Vitamin D and calcium supplementation seems to be a very promising treatment and preventing option. It has been stated that several quantifiable variables of vitamin D receptor are associated with MS, which suggests a possible clinical immunomodulatory application of vitamin D for MS patients (Al-Temaimi *et al.*, 2015). The significant role of vitamin D in pathological processes occurring in CNS has been documented by other authors as well (Gu *et al.*, 2015). An anti-inflammatory effect of vitamin D is unclear. It has been showed that high-dose oral vitamin D_3 supplementation in patients with the relapsing-remitting MS prominently increases serum 25-OHD levels without affecting the markers of systemic inflammation (Røsjø *et al.*, 2015). It can be concluded that future research is definitely needed in this field in order to establish helpful recommendations. Due to this fact, these days clinicians have to follow general recommendations for osteoporosis treatment like guidelines of The UK National Institute for Health and Care Excellence (NICE) or National Osteoporosis Society (NOS) (Aspray *et al.*, 2014; Gupta *et al.*, 2014; Kmietowicz, 2008). Clinical evaluation in all patients with MS should include the assessment of clinical risk factors of osteoporosis and fractures. First of all, non-pharmacological methods (smoking cessation, reducing alcohol intake, an increased physical activity) are needed. Clinicians and patients should also consider the resistance training which helps to increase bone strength and muscle power as well as reduces the risk of falling as it improves keeping the balance. Furthermore, optimizing vitamin D levels and calcium supplementation are essential to maintain the health of bones and their physiological structure (Ishimi, 2015). Where rapid correction of vitamin D deficiency is required (cases of symptomatic bone diseases), it should be given at doses of 800–2000 IU daily (occasionally up to 4,000 IU daily), but higher doses might also be needed (Aspray *et al.*, 2014). Vitamin D deficiency should also be corrected by encouraging patients to obtain enough sunlight exposure and by prescribing vitamin D at a dose of 600 IU/day for those aged <70 years and 800 IU/day for those aged >70 years until serum 25-OHD levels reach at least 50 nmol/L. Gupta *et al.* (2014) also state in their review article that even higher intake of up to 4,000 IU, with repeated testing of vitamin D levels to reach 30–40 ng/mL, is suggested by recent recommendations specific for MS patients. Gibson and Summers (2011) suggest that people with an EDSS ≥6 and those who are housebound should have serum 25-OHD status determined and, if necessary, treated with a target 25-OHD level of at least 50 nmol/L. The authors of the recently published Global Consensus Recommendations on Prevention and Management of Nutritional Rickets define 25-OHD sufficiency as its serum level >50 mmol/L, insufficiency as 30–50 mmol/L and deficiency as <30 mmol/L. In their opinion, for the prevention of rickets and osteomalacia, all children beyond 12 months of age and adults need to meet their nutritional requirements for vitamin D through diet and/or supplementation, which is at least 600 IU/day (15 μg), as recommended by the Institute of Medicine (IOM). For the treatment of nutritional rickets, the minimal recommended dose of vitamin D is 2,000 IU/day (50 μg) for a minimum of 3 months (Munns *et al.*, 2016). The sufficient calcium intake is 800 mg daily in children aged between 1 and 10 years old, 1000–1200 mg in youth and adults, 1200–1300 mg in pregnant women, during lactation, after menopause and in the elderly (Głuszko and Tłustochowicz, 2013). Certainly, treatment with

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bisphosphonates and other drugs is a very effective intervention in osteoporosis. Due to this fact, there are detailed recommendations concerning these therapeutic methods (Aspray *et al.*, 2014; Kmietowicz, 2008). However, it is not the topic of our article, thus it will not be discussed herein. Although, there are no official recommendations on the treatment of osteoporosis in MS patients, one can find publications where authors propose their own algorithms for the management of bone health in MS patients (Gupta *et al.*, 2014).

DISCUSSION AND CONCLUSIONS

It is certain that unified guidelines on the management of osteoporosis in patients suffering from multiple sclerosis are needed. Thanks to a mounting number of different conclusions provided in recent publications, we can hope that establishing such recommendations will occur in the nearest future. However, these days clinicians have to follow the results and conclusions of only single studies, often based on small populations. They should focus not only on the treatment of osteoporosis in patients with multiple sclerosis, but also on predicting, diagnosing and preventing from osteoporosis in this group of patients. The most popular and useful tool for fracture prediction is Fracture Risk Assessment Tool (FRAX® tool). It can be used as an initial and rough method for estimation and monitoring the risk of osteoporosis in MS patients. However, it does not take into account a number of secondary causes for osteoporosis that an individual patient has, which arguably limits its usefulness in MS. Apart from the FRAX® calculator, other preferential marker of fracture risk is Dual Energy X-ray Absorptiometry (DXA). People with MS should have BMD measurements performed within a couple of years following the diagnosis identifying a reduced BMD. In addition, those with frequent relapses and/or rapidly progressive disability should be offered repeated DXA screening because of a higher risk of reduced BMD associated with immobility. No evidence provides guidelines as to the frequency of repeated DXA scanning in people with MS, although the frequency of three to five years has been suggested (Kampman *et al.*, 2011). There is a strong need to spread the knowledge on this issue through clinicians by organising topical conferences and lectures. It would probably contribute to a better management of these patients.

In conclusion, the relationship between multiple sclerosis and osteoporosis is a significant clinical problem which remains not commonly known and widely discussed among clinicians. Fortunately, many authors are conducting valuable research projects, publishing helpful results and conclusions as well as creating large, comprehensive meta-analyses. Thanks to them our knowledge on this interesting issue is still growing. In our article we aimed at presenting and summarising the most important clinical aspects of the relationship between these two diseases. We hope that clinicians will find it valuable and helpful in their practice.

Conflict of interest

The authors report no conflict of interest relevant to the manuscript.

References

Al-Temaimi RA, Al-Enezi A, Al-Serri A *et al.*: The association of vitamin D receptor polymorphisms with multiple sclerosis in a case-control study from Kuwait. PLoS One 2015; 10: e0142265.

Aspray TJ, Bowring C, Fraser W *et al.*; National Osteoporosis Society: National Osteoporosis Society vitamin D guideline summary. Age Ageing 2014; 43: 592–595.

Batista S, Teter B, Sequeira K *et al.*: Cognitive impairment is associated with reduced bone mass in multiple sclerosis. Mult Scler 2012; 18: 1459–1465.

Cosman F, Nieves J, Komar L *et al.*: Fracture history and bone loss in patients with MS. Neurology 1998; 51: 1161–1165.

Dovio A, Perazzolo L, Osella G *et al.*: Immediate fall of bone formation and transient increase of bone resorption in the course of high-dose, short-term glucocorticoid therapy in young patients with multiple sclerosis. J Clin Endocrinol Metab 2004; 89: 4923–4928.

Gibson JC, Summers GD: Bone health in multiple sclerosis. Osteoporos Int 2011; 22: 2935–2949.

Głuszko P, Tłustochowicz W: Osteoporoza. In: Gajewski P, Szczeklik A (eds.): Interna Szczeklika 2013. 5th ed., Medycyna Praktyczna, Kraków 2013: 1938–1943.

Gu SG, Wang CJ, Zhao G *et al.*: Role of vitamin D in regulating the neural stem cells of mouse model with multiple sclerosis. Eur Rev Med Pharmacol Sci 2015; 19: 4004–4011.

Guenter W, Jabłońska J, Bieliński M *et al.*: Neuroimaging and genetic correlates of cognitive dysfunction in multiple sclerosis. Psychiatr Pol 2015; 49: 897–910.

Gupta S, Ahsan I, Mahfooz N *et al.*: Osteoporosis and multiple sclerosis: risk factors, pathophysiology, and therapeutic interventions. CNS Drugs 2014; 28: 731–742.

Hearn AP, Silber E: Osteoporosis in multiple sclerosis. Mult Scler 2010; 16: 1031–1043.

Hollenbach JA, Oksenberg JR: The immunogenetics of multiple sclerosis: a comprehensive review. J Autoimmun 2015; 64: 13–25.

Ishii M, Egen JG, Klauschen F *et al.*: Sphingosine-1-phosphate mobilizes osteoclast precursors and regulates bone homeostasis. Nature 2009; 458: 524–528.

Ishimi Y: Osteoporosis and lifestyle. J Nutr Sci Vitaminol (Tokyo) 2015; 61 Suppl: S139–S141.

Kampman MT, Eriksen EF, Holmøy T: Multiple sclerosis, a cause of secondary osteoporosis? What is the evidence and what are the clinical implications? Acta Neurol Scand Suppl 2011: 44–49.

Kmietowicz Z: NICE publishes osteoporosis guidance after more than six years of consultation. BMJ 2008; 337: a2397.

Lambrinoudaki I, Patikas E, Kaparos G *et al.*: Vitamin D receptor Bsm1 polymorphism, calcium metabolism and bone mineral density in patients with multiple sclerosis: a pilot study. Neurol Sci 2013; 34: 1433–1439.

Marrie RA, Cutter G, Tyry T *et al.*: A cross-sectional study of bone health in multiple sclerosis. Neurology 2009; 73: 1394–1398.

McLean RR: Proinflammatory cytokines and osteoporosis. Curr Osteoporos Rep 2009; 7: 134–139.

van der Mei IA, Ponsonby AL, Dwyer T *et al.*: Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. J Neurol 2007; 254: 581–590.

Munns CF, Shaw N, Kiely M *et al.*: Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. Horm Res Paediatr 2016; 85: 83–106.

Muris AH, Rolf L, Broen K *et al.*: A low vitamin D status at diagnosis is associated with an early conversion to secondary progressive multiple sclerosis. J Steroid Biochem Mol Biol 2015. DOI: 10.1016/j.jsbmb.2015.11.009.

Niino M, Miyazaki Y, Fukazawa T *et al.*: Vitamin D and latitude as environmental factors in multiple sclerosis. Nihon Rinsho 2014; 72: 1924–1929.
Polachini CR, Spanevello RM, Zanini D *et al.*: Evaluation of delta-aminolevulinic dehydratase activity, oxidative stress biomarkers, and vitamin D levels in patients with multiple sclerosis. Neurotox Res 2016; 29: 230–242.
Ramanujam R, Hedström AK, Manouchehrinia A *et al.*: Effect of smoking cessation on multiple sclerosis prognosis. JAMA Neurol 2015; 72: 1117–1123.
Røsjø E, Steffensen LH, Jørgensen L *et al.*: Vitamin D supplementation and systemic inflammation in relapsing-remitting multiple sclerosis. J Neurol 2015; 262: 2713–2721.
Triantafyllou N, Lambrinoudaki I, Thoda P *et al.*: Lack of association between vitamin D levels and bone mineral density in patients with multiple sclerosis. J Neurol Sci 2012; 313: 137–141.
Veldman CM, Cantorna MT, DeLuca HF: Expression of 1,25-dihydroxyvitamin D_3 receptor in the immune system. Arch Biochem Biophys 2000; 374: 334–338.
Weinstock-Guttman B, Gallagher E, Baier M *et al.*: Risk of bone loss in men with multiple sclerosis. Mult Scler 2004; 10: 170–175.
Wolski H, Drwęska-Matelska N, Seremak-Mrozikiewicz A *et al.*: [The role of Wnt/β-catenin pathway and LRP5 protein in metabolism of bone tissue and osteoporosis etiology]. Ginekol Pol 2015; 86: 311–314.
Zorzon M, Zivadinov R, Locatelli L *et al.*: Long-term effects of intravenous high dose methylprednisolone pulses on bone mineral density in patients with multiple sclerosis. Eur J Neurol 2005; 12: 550–556.

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