*Tomasz Targowski

Differences in the metabolism of vitamin D in sarcoidosis

Odmienności metabolizmu witaminy D w sarkoidozie

Department of Geriatrics, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw
Head of Department: Professor Tomasz Targowski, MD, PhD, ScD

Keywords
sarcoidosis, vitamin D, alveolar macrophages

Słowa kluczowe
sarkoidoza, witamina D, makrofagi pęcherzykowe

Conflict of interest
Konflikt interesów
None
Brak konfliktu interesów

Address/adres:
*Tomasz Targowski
Department of Geriatrics
National Institute of Geriatrics,
Rheumatology and Rehabilitation
ul. Spartańska 1, 02-637 Warszawa
tel. +48 (22) 844-42-41, wew. 161
klinika.geriatrii@spartanska.pl

S u m m a r y

It is well known that low concentrations of vitamin D in the body increase the risk of osteoporosis, however excessive intake of vitamin D may also contribute to disorders of calcium-phosphate metabolism and bone mineralization. According to literature data, loss of bone mass is present in up to 80% of patients suffering from the interstitial lung diseases, including sarcoidosis. Hypercalcemia and hypercalciuria due to excessive activation of vitamin D are relatively common symptoms associated with granulomatous diseases such as sarcoidosis. The article describes differences in the metabolism of vitamin D in patients with sarcoidosis, as well as the potential clinical significance of this disorder.

S t r e s z c z e n i e

Powszechnie wiadomo, że niskie stężenia witaminy D w organizmie zwiększają ryzyko osteoporozy, niemniej nadmierna podaż witaminy D również może przyczyniać się do zaburzeń gospodarki wapniowo-fosforanowej i mineralizacji kośćca. Według danych z literatury utratę masy kostnej obserwuje się u blisko 80% pacjentów chorujących na choroby śródmiąższowe płuc, w tym na sarkoidozę. Hiperkalcemia i hiperkalciuria z powodu nadmiernej aktywacji witaminy D są stosunkowo częstymi objawami towarzyszącymi chorobom ziarniniakowym, takim jak sarkoidoza. W artykule opisano odmienności metabolizmu witaminy D u chorych na sarkoidozę, jak również potencjalne znaczenie kliniczne tego zaburzenia.

Interstitial lung disease is often accompanied by disorders of vitamin D metabolism and related to them disorders of bone mineralization. According to literature data, loss of bone mass is present in up to 80% of patients suffering from the above mentioned respiratory diseases, of which osteoporosis is approx. 44% of the cases (1). Interstitial lung diseases are quite heterogeneous collection of about 200 diseases of different etiology, and clinical course, divided arbitrarily several years ago in four main groups: a disease of known cause (e.g. side effects of drugs or diseases of the connective tissue), idiopathic interstitial pneumonia, granulomatous diseases, and other (e.g. pulmonary eosinophilia, lymphangioleiomyomatosis, etc.) (2). Sarcoidosis takes second place on the list of the most often occuring interstitial diseases of the respiratory system, after idiopathic pulmonary fibrosis and before allergic alveolitis (2).

Sarcoidosis occurs in all ages, with a peak incidence among young adults (20-40 years) (3). Women and black people are particularly exposed. In some highly industrialized countries (e.g. Sweden) can be observed the second peak incidence in women over 50 years of age. Children are rarely suffering from sarcoidosis, and it is rather benign (2, 3). Not becoming caseous granuloma that are composed of epitheloid cells, multinucleated giant cells, macrophages and lymphocytes are typical pathomorphological changes in sarcoidosis. Epithelioid cells emerging from activated macrophages and multinucleated giant cells occupy the central part of the granuloma, and the helper CD4 lymphocytes gather around them. Sarcoidosis is a systemic disease, and sarcoidal granulomas may appear in virtually every organ of the body, yet most frequently (in 90% of cases) can be found in pulmonary parenchyma (2, 4).

In sarcoidosis, as in the case of other interstitial lung diseases for example idiopathic pulmonary fibrosis and other chronic diseases, e.g. rheumatoid arthritis, there is an increased risk of bone mineralization

disorders (4, 5). According to literature data, nearly 55% of patients with sarcoidosis without accompanying chronic diseases have reduced bone mineral density (osteopenia or osteoporosis). Furthermore, in nearly a quarter of patients with this disease with normal density of bone mass may occur low-energy fractures of the skeletal system (5).

Disorders of bone mineralization in patients with sarcoidosis result from the possible need for prolonged systemic glucocorticoid use in therapy and chronic systemic inflammatory response accompanying disease (4, 5). In addition, the condition of the bone system is affected by (fairly specific for sarcoidosis) pathomechanisms of calcium and vitamin D metabolism disorders primarily related with non-renal production of excessive amounts of active metabolites of vitamin D (calcitriol) by sarcoidal granulomas which results in hypercalcemia and hypercalciuria. Less often abnormal bone mineralization in sarcoidosis results from direct seizure of the bone system by sarcoidal granulation tissue because, according to the literature, direct damage to the bone affected by the disease occurs in about 1.5 to 13% of patients with sarcoidosis (7, 8).

For the first time the case of hypercalcemia in patients with sarcoidosis was described in 1939 in a patient who consumed cod liver oil (9). In 1983, Adams et al. (10) described non-renal production of active vitamin D metabolites by activated alveolar macrophages that are forming sarcoidal granulation tissue. At about the same time calcitriol [1,25$(OH)_2$D] receptor on the surface of activated lymphocytes was also detected (11). According to the present state of knowledge stimulation of sarcoidal granulation tissue macrophages and conversion of the metabolically inactive ergocalcitriol [25(OH)D] into calcitriol are mainly influenced by interferon-gamma (IFN-gamma) and tumor necrosis factor-alpha (tumor necrosis factor-alpha – TNF-alpha) which are locally produced in sarcoidal granulomas by macrophages and activated lymphocytes (12, 13). It has been shown, inter alia, that IFN-gamma present in the sarcoidal granulation tissue regulates the autonomous production of 1-alpha hydroxylase, the enzyme responsible for conversion of ergocalcitriol into the active metabolite of vitamin D – calcitriol (12) in sarcoidal granulation tissue. While the active vitamin D metabolites produced by alveolar macrophages and kidneys are not significantly different in their biological activity, there are substantial differences in the activity of hydroxylases produced in lungs and urinary tract. And so, in patients with sarcoidosis synthesis of hydroxylase 25(OH)D-24 by alveolar macrophages to catalyze the conversion of calcitriol [1,25$(OH)_2$D] into an inactive metabolite of 24,25$(OH)_2$D, in contrast to the 25-hydroxylase (OH)-D-24 produced by kidneys begins to be stimulated only at very high, non-physiological concentrations of calcitriol which can significantly affect the calcium-phosphate metabolism in patients with sarcoidosis (14). Baughman et al. (15) evaluating disorders of metabolism of vitamin D (in a group of 261 patients) and calcemia in serum (in the group of 1606 patients) in patients with sarcoidosis found elevated levels of active form of vitamin D calcitriol [1,25$(OH)_2$D] in the serum of 11% of the patients and Hypercalcemia associated with sarcoidosis in 6% of the patients.

It is worth noting that in this study reduction in the concentration of the inactive metabolite of vitamin D [ergocalcitriol; 25(OH)D] in up to 80% of patients was observed (15). You should take this into account when performing the measurement of the total concentration of vitamin D in patients with sarcoidosis, because despite normal or reduced level of the total concentration of vitamin, concentration levels of the active metabolite in serum can be high. Excessive urinary calcium excretion in patients with sarcoidosis is observed even in 40% of cases, thus much more often than in hypervitaminosis D and hypercalcaemia (4, 16).

It is also worth noting that although black people are more susceptible to sarcoidosis, hypercalciuria in the course of the disease is more common in white people (17). It is due to decreased skin synthesis of vitamin D in black people (18). In the literature there are reported cases of acute kidney injury in the course of hypercalcemia associated with sarcoidosis, especially after exposure to intense sunlight, which means metabolism of vitamin D disorder(18, 19). In addition, disorders of calcium-phosphate metabolism in sarcoidosis resulting even in calcification of soft tissues may increase during excessive consumption of Coca-Cola (the source of large quantities of phosphates), especially in the summer (18). Therefore, patients with sarcoidosis should be cautiously supplemented in diet not only with calcium, but phosphates as well. Direct damage to the urinary tract through the development of sarcoidal granulation tissue in the renal parenchyma is very rare (4).

Because of the autonomous production of vitamin D, the question is still unclear whether substitution of calcium and vitamin D in patients with sarcoidosis, requiring chronic glucocorticosteroid therapy (in contrast for example to explicitly recommended supplementation of these substances in patients with rheumatoid arthritis treated with glucocorticosteroid) is justified (20). Saidenberg-Kermanac'h et al. (5) studying 142 patients with sarcoidosis (mostly Caucasians) have found that one of the factors of higher risk of osteoporotic fractures and decreased bone mineral density among respondents was low intake of calcium, but on the other hand desirable, consistent with standards concentration of 25(OH)D levels (> 20 ng/mL) was associated with more than double risk of fractures and four times higher risk of lowering BMD (Bone Mineral Density) for at least one standard deviation compared with patients whose serum relatively lacked 25(OH)D (concentration range of 10-20 ng/ml). What is more interesting, although in this study vitamin D supplementation was associated with increased concentration of 25(OH)D in serum in patients with sarcoidosis, it had no effect on the value of calcemia (5). On the other hand Bolland

et al. (21) observed that in patients with sarcoidosis, regardless initial vitamin D concentrations in serum, long-term disorders of bone mineralization are relatively small and unless the patients are treated with glucocorticoids, there is no need for routine monitoring of the BMD values.

Patients with more advanced sarcoidosis usually have higher concentration of active metabolites of vitamin D (15, 20). It is believed that the autonomous synthesis of vitamin D in sarcoidosis may result from its properties of modulating the activity of the immune system. Vitamin D receptor was found on the surface of many cells involved in inflammatory reactions, such as activated T and B lymphocytes, macrophages, or dendritic cells (11, 18). It was demonstrated that the active metabolite of vitamin D inhibits proliferation of T helper lymphocytes which produce interferon-gamma and interleukin-2 in sarcoidal granulation tissue as well as stimulate macrophages (22).

Furthermore, it has been shown that activation of the macrophage Toll-like receptors (TLRs) playing an important role in the mechanisms of human innate immunity causes increased expression of vitamin D receptors (VDRs) and genes for hydroxylase 1, which in turn leads to stimulation of the cathelicidin peptide (cathelicidin) having bactericidal effect on intracellular pathogens like tuberculous bacilli (23). These data suggest a significant share of vitamin D in the regulation of immune processes associated with the formation of granulomas, especially that there are many pathognomonic similarities between sarcoidosis and tuberculosis and involvement of mycobacteria in the initiation of sarcoidosis has been discussed for many years (24-26). Vitamin D being crucial in the mechanisms of cellular immunity may be proved by the fact that patients take sarcoidosis most often in winter, when the concentration of vitamin D is the lowest in the body, moreover, those who suffer more often are Afro-Americans, who have a greater tendency to deficiency of vitamin D compared with Caucasians (27, 28).

Reassuming, autonomous synthesis of active vitamin D metabolites in patients with sarcoidosis can be associated with self-regulation of the inflammatory response of the body to still unknown etiological factor of the disease. So far it has not been resolved clearly whether in patients with sarcoidosis with impaired bone density substitution of vitamin D is clinically justified.

BIBLIOGRAPHY

1. Alhamad EH, Nadama R: Bone mineral density in patients with interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis 2015; 32(2): 151-159.
2. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002; 165(2): 277-304.
3. Wu JJ, Rashcovsky Schiff K: Sarcoidosis. Am Fam Physician 2004; 70: 321-322.
4. Iannuzzi MC, Rybicki BA, Teirstein AS: Sarcoidosis. N Engl J Med 2007; 357(21): 2153-2165.
5. Saidenberg-Kermanac'h N, Semerano L, Nunes H et al.: Bone fragility in sarcoidosis and relationships with calcium metabolism disorders: a crosss sectional study on 142 patients. Arthrithis Res Ther 2014; 16: R78.
6. Goldring SR, Gravallesse EM: Mechanisms of bone loss in inflammatory arthritis: diagnosis and therapeutic implications. Arthritis Res 2000; 2: 33-37.
7. Sparks JA, McSparron JI, Shah N et al.: Osseous sarcoidosis: Clinical characteristics, treatment, and outcomes – Experience from a large, academic hospital. Seminars in Arthritis and Rheumatism 2014; 44: 371-379.
8. Wilcox A, Bharadwaj P, Sharma OP: Bone sarcoidosis. Curr Opin Rheumatol 2000; 12: 321-330.
9. Harrell GT, Fisher S: Blood chemical changes in Boeck's sarcoid with particular reference to protein, calcium and phosphatase values. J Clin Invest 1939; 18: 687-693.
10. Adams J, Sharma O, Gacad M, Singer F: Metabolism of 25-hydroxyvitamin D_3 by cultured pulmonary alveolar macrophages in sarcoidosis. J Clin Invest 1983; 72: 1856-1860.
11. Sharma OP: Vitamin D and sarcoidosis. Curr Opin Pulm Med 2010; 16: 487-488.
12. Reichel H, Koeffler HP, Tobler A, Norman AW: 1 alpha, 25-Dihydroxyvitamin D_3 inhibits gamma-interferon synthesis by normal human peripheral blood lymphocytes. Proc Natl Acad Sci USA 1987; 84: 3385-3389.
13. Stoffels K, Overbergh L, Giulietti A et al.: Immune regulation of 25-hydroxyvitamin-D_3-1alpha-hydroxylase in human monocytes. J Bone Miner Res 2006; 21: 37-47.
14. Rizzato G: Clinical impact of bone and calcium metabolism changes in sarcoidosis. Thorax 1998; 53(5): 425-429.
15. Baughman RP, Janovcik J, Ray M et al.: Calcium and vitamin D metabolism in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2013; 30(2): 113-120.
16. Berliner AR, Haas M, Choi MJ: Sarcoidosis: the nephrologist's perspective. Am J Kidney Dis 2006; 48: 856-870.
17. Baughman RP, Teirstein AS, Judson MA et al.: Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001; 164: 1885-1889.
18. Demetriou ET, Pietras SM, Holick MF: Hypercalcemia and soft tissue calcification owing to sarcoidosis: the sunlight-cola connection. J Bone Miner Res 2010; 25(7): 1695-1699.
19. Dierkes-Globish A, Schneiderhan W, Mohr HH: Acute renal failure due to hypercalcemia and peripheral polyneuropathy – rare manifestations of sarcoidosis. Med Klin 2000; 95(10): 583-586.
20. Baughman RP, Lower EE: Goldilocks, vitamin D and sarcoidosis. Arthritis Res Ther 2014; 16: 111.
21. Bolland MJ, Wilsher ML, Grey A et al.: Bone density is normal and does not change over 2 years in sarcoidosis. Osteoporos Int 2015; 26(2): 611-616.
22. Bikle D: Nonclassic actions of vitamin D. J Clin Endocrinol Metab 2009; 94: 26-34.
23. Liu PT, Stenger S, Li H et al.: Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006; 311: 1770-1773.
24. Gupta D, Agarwal R, Aggarwal AN, Jindal SK: Sarcoidosis and tuberculosis: the same disease with different manifestations or similar manifestations of different disorders. Curr Opin Pulm Med 2012; 18(5): 506-516.
25. Richmond BW, Drake WP: Vitamin D, innate immunity, and sarcoidosis granulomatous inflammation: insights from mycobacterial research. Current Opinion in Pulmonary Medicine 2010; 16: 461-464.
26. Mortaz E, Adcock IM, Barnes PJ: Sarcoidosis: Role of non-tuberculosis mycobacteria and Mycobacterium tuberculosis. Int J Mycobacteriol 2014; 3(4): 225-229.
27. Ginde AA, Liu MC, Camargo CA: Demographic differences and trends of vitamin D insufficiency in the US population, 1998-2004. Arch Int Med 2009; 169: 626-632.
28. Newman LS, Rose CS, Maier LA: Sarcoidosis. N Engl J Med 1997; 336: 1224-1235.

received/otrzymano: 01.09.2016
accepted/zaakceptowano: 22.09.2016