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Vitamin D in rheumatoid arthritis

Witamina D w reumatoidalnym zapaleniu stawów

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S u m m a r y

The aim of this study was to summarize the publications on relationship between vitamin D and development and outcomes of rheumatoid arthritis (RA). We did a systematic search of genetic, epidemiological, observational and intervention studies and meta-analyses that assessed the effect of vitamin D on the risk and outcomes of rheumatoid arthritis. Several genotype variants of vitamin D receptor (VDR) have been linked to early RA onset and lower bone mass in RA patients in some studies, but the results are dissimilar in different examined populations. Epidemiological studies show possible association between lower sun exposure and lower total vitamin D intake and the risk of RA development. Observational and intervention studies searching association between vitamin D serum concentration and disease activity have produced conflicting results. Despite a growing number of publications the evidence of a clear role of vitamin D in RA is still rather weak. Whether low 25(OH)D serum concentration is the cause or simply the result of a chronic disease is not known. Further randomized controlled trials are needed to clarify the role of vitamin D supplementation in RA treatment.

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

Celem pracy było podsumowanie publikacji na temat związków witaminy D z rozwojem i przebiegiem reumatoidalnego zapalenia stawów (RZS). Dokonaliśmy przeglądu badań genetycznych, epidemiologicznych, obserwacyjnych, interwencyjnych oraz metaanaliz, w których oceniano wpływ witaminy D na ryzyko wystąpienia i przebieg reumatoidalnego zapalenia stawów. W badaniach stwierdzono związek niektórych wariantów genowych receptora witaminy D (VDR) z wczesnym początkiem RZS i niską masą kostną u chorych na RZS, jednak wyniki różniły się w zależności od badanych populacji. Badania epidemiologiczne wskazują na możliwy związek pomiędzy mniejszą ekspozycją na promieniowanie słoneczne i mniejszym całkowitym spożyciem witaminy D a ryzykiem rozwoju RZS. Badania obserwacyjne i interwencyjne na temat związku stężenia witaminy D z aktywnością choroby przynoszą sprzeczne rezultaty. Pomimo rosnącej liczby prac nie ma nadal przekonujących dowodów na istotną rolę witaminy D w RZS. Nie wiadomo, czy niskie stężenie 25(OH)D w surowicy stanowi przyczynę, czy jedynie skutek przewlekłej choroby. Aby ocenić znaczenie suplementacji witaminy D w leczeniu RZS konieczne jest przeprowadzenie dalszych badań randomizowanych.

Conflict of interest
Konflikt interesów
None
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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune systemic disease characterized predominantly by synovial inflammation, leading to joint destruction. RA affects up to 1% of the population in the world and is associated with reduced life expectancy (1). The synovium in RA transforms into inflammatory tissue, called pannus, which produces several proinflammatory mediators and invades cartilage and bone. Pannus formation is caused by the proliferation of fibroblast-like synovial cells and synoviocytes, angiogenesis, infiltration of macrophages and lymphocytes and migration of polymorphonuclear cells to the synovial tissue (2). Interleukin 1 (IL-1), tumor necrosis factor (TNF-α) and interleukin 6 (IL-6) play a primary role in mediating this process. One of the important mechanisms of RA pathophysiology is the imbalance between Th1 and Th2 response with Th1 predominance (interleukin 2 and interferon γ excretion). The other significant inflammatory pathway is associated with Th17 cells and characterized by production of IL-17A, IL-17F, TNF and IL-6 (3). The risk factors for RA development involve

the combination of genetic and environmental components. The most important genetic factor is associated with the major histocompatibility complex antigen HLA-DRB1 and shared epitope, which is closely related to serum presence of rheumatoid factor (RF) or anti-citrullinated peptide antibodies (a-CCP) (4, 5). Of the environmental stimuli that contribute, the best defined is smoking, which can interact with genes to increase disease susceptibility (4). One of the other possible environmental factors is vitamin D. Despite being a crucial element of calcium homeostasis and bone mineralization, vitamin D also plays an important role in immune system. The expression of vitamin D receptor (VDR) was discovered on antigen-presenting cells, dendritic cells and lymphocytes. VDR has been demonstrated in the rheumatoid synovium and macrophages derived from RA patients are capable to vitamin D synthesis (6). Active metabolite of vitamin D, calcitriol (1,25-dihydroxyvitamin D) can inhibit the macrophage synthesis of interleukines 1, 6, 12 and TNF-α, suppress the interleukin 2 secretion by Th1 lymphocytes and decrease antigen-presenting activity of macrophages – therefore restoring balance between Th1, Th17 and Th2 cells (7). Furthermore, calcitriol inhibits plasma-cell differentiation and B-cell proliferation (8). Vitamin D deficiency is more common in autoimmunological diseases than in general population (9). These observations were the reason for numerous studies on the role of vitamin D deficiency in the occurrence, activity and severity of RA.

GENETIC STUDIES

There are controversial results of VDR polymorphisms according to the association with RA in different populations. Polymorphism of VDR receptor has been linked to accelerated bone loss in RA (alleles TaqI and BsmlB) (6, 10) and early RA onset (alleles FokI and TaqI) in Hungary (6). Among Spanish postmenopausal women with RA the bb genotype of the BsmI polymorphism of the VDR gene was associated with less severe disease (11). In a previous study from the same country RA women with the presence of the shared epitope (HLA-DRB1) and BB/tt genotype of the VDR (alleles TaqI and Bmsl) had the earliest disease onset (12). FokI polymorphism was associated with RA in French, North America Native and Egyptian patients (13-15). A significant association was found between lower hip bone mass Density (BMD) and genotype variants of VDR (BsmI) in RA Egyptian women with osteoporosis (16). The case-control study in German generation however showed no association between VDR polymorphism and RA (14).

ANIMAL MODELS AND HUMAN *IN VITRO* STUDIES

An importance of locally acting vitamin D metabolites have been shown in some studies of joint inflammation. The one of the first discoveries was the inhibition of collagen-stimulated arthritis in mice (16). Calcitriol was shown to inhibit invasive properties of fibroblast-like synoviocytes in tissue cultures from RA patients (18). VDR deficient mice have developed a more aggressive TNF-α mediated arthritis than the mice with normal vitamin D signaling (19). TNF-α blockade required the presence of calcitriol to effectively suppress inflammation in synovial tissue cultures by inhibiting Th17 activity (20).

EPIDEMIOLOGICAL OBSERVATIONS

People living at the highest latitudes have a higher risk of RA, which can be due to lower ultraviolet-stimulated vitamin D skin production (21). In two large cohort studies (the Nurses' Health study I and II) UV-B exposure was associated with lower RA risk, however dietary vitamin D intake had no influence on RA risk (21, 22). Oppositely, in Iowa Women's Health Study, including large cohort of elderly women, greater vitamin D intake showed an inverse correlation with RA incidence (23). Finally, after the meta-analysis, a significant association between total vitamin D intake and RA incidence was confirmed (24). Another large cohort study revealed that winter onset of RA is an independent factor for the early progression of joint damage (25). Studies of vitamin D serum concentration have been conducted around the world and, surprisingly, there are more studies suggesting no difference between RA and controls (26-29). Moreover no relationship was found between 25(OH)D and RF and a-CCP levels, thought to predict the disease onset (30).

VITAMIN D AND RA ACTIVITY

There is a growing number of studies of vitamin D and disease activity, but up till now they have produced conflicting results. No seasonal correlation was observed between 25(OH)D serum levels and RA activity (31). In the large multicenter study Rossini et all have found negative correlation between 25(OH)D and disease activity (DAS28), Health Assessment Questionnaire Disability Index (HAQ) and Mobility activities of daily living. Lower serum 25(OH)D levels were associated with lack of remission and poor response to therapy (28). The negative association between vitamin D level and clinical parameters, such as: tender and swollen joint count, pain degree, HAQ scores and laboratory measures (SR, CRP, serum concentration of inflammatory cytokines) have been described in several studies (32-34). However the other studies have not confirmed these findings. Two studies demonstrated no correlation between the DAS28 and vitamin D when VAS scale was excluded (patients' visual analogue scale assessing disease activity) (35, 36). Vitamin D level did not correlated with disease activity measures in golimumab and rituximab trials (37, 38). There are few controlled trials assessing the effects of vitamin D supplementation on disease activity. Comparison of triple disease modifying antirheumatic drug (DMARD) therapy and 500 IU 1,25(OH)D_3 with calcium versus triple DMARD and calcium alone resulted only in significant pain reduction in vitamin D group (39).

CONCLUSIONS

Most of the studies suggest the association between low serum vitamin D level and high disease activity in RA. However whether vitamin D deficiency is a cause or a consequence of the disease remains unclear. Randomized controlled trials are needed to find out if vitamin D supplementation plays an important role in RA treatment.

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