REVISTA BRASILEIRA DE REUMATOLOGIA

www.reumatologia.com.br

SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Brief communication

Vitamin D levels in ankylosing spondylitis: Does deficiency correspond to disease activity?

Gabriel G. Pokhai, Sabiha Bandagi, Adriana Abrudescu*

Department of Medicine, Division of Rheumatology, Icahn School of Medicine at Mount Sinai, Queens Hospital Center, New York, NY, USA

ARTICLE INFO

Article history:
Received 23 December 2013
Accepted 19 March 2014

Keywords:
Ankylosing Spondylitis
Vitamin D
Autoimmune
Inflammation
BASDAI

ABSTRACT

Ankylosing spondylitis (AS) is an inflammatory disorder that presents with arthritis of the axial skeleton, including sacroiliac joints. Vitamin D is a secosteroid hormone with a long-established role in calcium and phosphate homeostasis, and in the regulation of bone formation and resorption. It is now known that vitamin D plays an immunosuppressive role in the body, and there is interest of late in the role of vitamin D in autoimmune diseases. Inflammation may be responsible for some of the loss of bone mineral density seen in AS. We reviewed the literature for studies assessing vitamin D level as a marker of AS disease activity and those examining vitamin D levels in AS in comparison to healthy controls. Four of 7 studies found a significant negative correlation between vitamin D levels and Bath Ankylosing Spondylitis Index (BASDAI), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). In a review of 8 case-control studies, the mean level of 25-hydroxyvitamin D_3 was 22.8 ± 14.1 ng/mL in 555 AS patients *versus* 26.6 ± 12.5 ng/mL in 557 healthy controls. When compared with a 2-sample t test, vitamin D levels were significantly higher in healthy controls ($p < 0.01$). We conclude that patients with AS appear to have lower vitamin D levels *versus* healthy controls; however, the cause is unclear. Existing studies do not demonstrate a consistent link between vitamin D levels and disease activity in AS. Further studies are in need to determine if a causative link exists between vitamin D deficiency and AS.

Níveis de vitamina D na espondilite anquilosante: a deficiência corresponde à atividade da doença?

Palavras-chave:
Espondilite anquilosante
Vitamina D
Autoimune
Inflamação
BASDAI

RESUMO

A espondilite anquilosante (EA) é um transtorno inflamatório que se apresenta com artrite da coluna vertebral, inclusive das articulações sacroilíacas. A vitamina D é um hormônio secosteroide com papel consagrado na homeostase do cálcio e do fosfato e na regulação da formação e reabsorção óssea. Atualmente, sabe-se que a vitamina D desempenha um papel imunossupressivo no organismo, e ultimamente tem havido interesse no papel dessa vitamina em doenças autoimunes. A inflamação pode ser responsável por parte da perda da

* *Corresponding author.*
E-mail: gabriel.pokhai@mountsinai.org (G.G. Pokhai).

0482-5004/$ - see front matter.
http://dx.doi.org/10.1016/j.rbr.2014.03.027

densidade mineral óssea observada em pacientes com EA. Revisamos a literatura em busca de estudos que avaliassem os níveis de vitamina D em pacientes com EA, em comparação com controles saudáveis. Quatro dos sete estudos chegaram a uma significativa correlação negativa entre os níveis de vitamina D e o instrumento *Bath Ankylosing Spondylitis Index* (BASDAI), velocidade de hemossedimentação (VHS) e proteína C reativa (PCR). Em uma revisão de oito estudos de caso-controle, o nível médio de 25-hidroxivitamina D_3 foi 22,8 ± 14,1 ng/mL em 555 pacientes com EA *versus* 26,6 ± 12,5 ng/mL em 557 controles saudáveis. Quando comparados com um teste *t* para duas amostras, os níveis de vitamina D estavam significativamente mais altos em controles saudáveis (p <0,01). Concluímos que pacientes com EA parecem ter níveis de vitamina D mais baixos *versus* controles saudáveis, mas a causa desse achado ainda não foi esclarecida. Os estudos já publicados não demonstram uma ligação consistente entre níveis de vitamina D e atividade da doença em pacientes com EA. Há necessidade de mais estudos que determinem se existe um elo causal entre deficiência de vitamina D e EA.

Introduction

Ankylosing spondylitis (AS) is an inflammatory disorder of unknown cause that features arthritis of the spine and sacroiliac joints, oligoarthritis of peripheral joints, and inflammation of tendons, ligaments, and joint capsule insertion sites. The onset of the disease usually begins in the second or third decade of life with a male to female prevalence of 3:1.[1] Patients generally experience a gradual onset of back stiffness and pain radiating to the buttocks with symptoms progressing in an ascending fashion. Peripheral arthritis of hips, shoulders and knees may be transient or permanent. Advanced disease can involve fusion of the entire spine. AS is correlated with HLA-B27 antigen positivity, and patients test negative for serum rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Disease activity in AS can be measured with non-specific inflammatory serum markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), or with a standardized questionnaire such as the bath ankylosing spondylitis disease activity index (BASDAI).

Vitamin D is a secosteroid hormone with a well-established role in calcium and phosphate homeostasis, and in the regulation of bone formation and resorption, however it is now known that vitamin D is much broader. Studies have shown vitamin D functions as an endogenous immunomodulator. Vitamin D alters gene expression that affects cellular functions, such as apoptosis, differentiation, and proliferation.[2] Alterations in vitamin D receptors have been linked to autoimmune conditions, with some studies suggesting an association between vitamin D deficiency and autoimmune disease.[3] As such, there has been increasing interest in studying vitamin D levels in patients with autoimmune conditions.

Osteoporosis is a well-known feature of AS, and studies have suggested that lower bone mineral density and higher bone turnover may be related to inflammation.[4] Thus it stands to reason that vitamin D levels may bear some relation to disease activity in AS. There have been a handful of clinical investigations over the last 20 years looking at what role vitamin D, or deficiency thereof, may play in AS. The aim of this review study is to summarize this research and to address two questions. First, do serum 25-hydroxyvitamin D_3 levels correspond to disease activity in patients with AS? Second, is there any difference between serum 25-hydroxyvitamin D_3 levels in patients with AS when compared to healthy control subjects?

Methods

A literature search was ran using the PubMed and Embase databases for English language peer-reviewed papers that examined either serum vitamin D levels in AS patients as compared to healthy controls, or the correlation between vitamin D levels in AS patients and disease activity. The keywords "vitamin D" and "ankylosing spondylitis" were used. All references cited by these papers were reviewed to locate additional studies not referenced in the aforementioned databases. Single case reports, review articles and studies that included patients with other autoimmune conditions other than AS in their analyses were excluded.

We identified 11 studies in total meeting these criteria,[4-12] among those, 8 were case-control studies, and 3 were case-only cross-sectional studies.

Vitamin D levels and disease activity

To evaluate the relationship between vitamin D levels and measures of disease activity, both cross-sectional and case-control studies were reviewed. Of the 11 studies that were retrieved, 7 studies examined the correlation between vitamin D levels and indicators of disease activity in AS. This included 6 suitable case-control studies and 1 cross-sectional case-only study. Collectively, this represented 573 patients, 82% of whom were male, with a mean age of 38.9 years.

The most common indicators of disease activity used were the bath ankylosing spondylitis index (BASDAI), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). All studies used the Spearman correlation coefficient to study the relationship between variables. For the purposes of this analysis, $p<0.05$ was taken as statistically significant. All studies compared disease activity with serum levels of 25-hy-

droxyvitamin D_3, except for the two studies by Lange that measured serum 1,25-dihydroxyvitamin D_3 levels.[4-5] The results are summarized in Table 1.

Four of 7 studies (encompassing 52% of the total patients) found a significant negative correlation between BASDAI and vitamin D levels, while the other 3 studies did not find a significant association. Significant negative correlations with vitamin D levels were noted for both ESR and CRP in 4 of 7 studies (encompassing 48% of total patients).

Vitamin D levels in ankylosing spondylitis

Eight case-control studies that compared vitamin D levels in a total of 555 AS patients and 557 healthy controls were identified. The mean age of these patients was 39.4 years, and 78.0% were male. Results are summarized in Table 2. The study by Yazmalar et al. studied vitamin D levels over summer and winter in the same set of patients.[11] As the vitamin D levels did not vary significantly between seasons, they were averaged.

Five of 8 studies found that patients with AS had significantly lower vitamin D levels than controls, while 3 studies found no significant difference. The average 25-hydroxyvitamin D level over all studies was (22.8±14.1) ng/mL in AS patients and (26.6±12.5) ng/mL in healthy controls. When compared with a 2-sample t test, the vitamin D levels were significantly higher in healthy controls (3.8±0.8 ng/mL, $p<0.01$). Only 6 of 8 studies compared ESR and CRP between healthy subjects and those with AS, but the serum levels of both markers were found to be significantly higher in patients with AS in all 6 of these studies.

Discussion

The vitamin D receptor gene is expressed in many immune cells.[13] Vitamin D regulates both innate and adaptive immunity suppressing adaptive immunity (B and T lymphocyte functions) and potentiates the innate response (monocytes, macrophages and antigen presenting cells).[14] The first aim of this review was to examine existing studies in order to determine if vitamin D levels in patients with AS correspond to disease activity.

The activity of many rheumatological diseases including AS can be measured with CRP and ESR, which are non-specific but provide some objective indication of inflammation. Several newer biomarkers which hope to offer better specificity are under investigation including matrix metalloproteinases (MMP-3), type II collagen epitopes, and interleukin-6 (IL-6).[15] The bath ankylosing spondylitis disease activity index (BASDAI) was developed in 1994 and provides a standardized method of assessing disease activity as it relates to patients' symptoms and quality of life. Although some newer models have been developed, BASDAI remains the most widely-used tool to assess disease activity in patients with AS.[16]

The studies in this analysis had conflicting data regarding the correlation of vitamin D levels with ESR, CRP and BASDAI scores. Also of note, most of the statistically significant correlations were weak ($r^2<0.6$). The existing studies are inconclusive as to whether serum vitamin D levels bear any significant correlation to systemic inflammation or disease activity in patients with AS. This echoes what has been seen in similar studies looking at activity of other rheumatological diseases.[3] The results in the literature are mixed, with some of studies finding an association between vitamin D levels and disease activity in SLE and RA, and other studies unable to reproduce these results.

The next question which we sought to address was whether vitamin D levels were different in patients with AS. Vitamin D insufficiency has been described as a pandemic, with as many as one billion people worldwide insufficient or deficient in vitamin D.[17] There is no universal consensus on what constitutes an ideal serum level of 25-hydroxyvitamin D_3. In a 2011 clinical practice guideline, the Endocrine Society stated an ideal serum level would be at least 30 ng/mL (75 nmol/L).[18] Serum levels between 21-29 ng/mL are defined as vitamin D insufficiency, and levels 20 ng/mL or below are considered vitamin D deficiency.

When data among the 8 studies we reviewed were pooled, it was found that patients with AS have significantly lower vitamin D levels as compared to healthy controls. The average vitamin D levels among AS patients in all 8 studies were insufficient or deficient. It is also interesting to note that mean vitamin D levels were also insufficient in the healthy controls in 5 of 8 studies.

Overall, the findings correspond with other cross-sectional studies which showed that deficient serum levels of vitamin

Table 1 – Correlation between vitamin D levels and disease activity in ankylosing spondylitis patients

First Author	Patients	Age (years)	Male %	R^2 Vit D vs. BASDAI	r^2 Vit D vs. VHS	r^2 Vit D. vs. PCR
Lange, 2005[4]	58	38.4[a]	65.5	-0.567	-0.57	-0.702
Lange, 2001[5]	70	38.4[a]	68.6	-0.547	-0.547	-0.711
Mermerci Baskan, 2010[6]	100	39.9 ± 10.9	75.0	NS	NS	NS
Arends, 2011[7]	128	41 ± 11.0	93.0	NS	NS	NS
Durmus, 2012[8]	99	36.8 ± 10.8	84.8	-0.304	-0.366	-0.344
Erten, 2013[9]	48	35.5 ± 10.0	79.2	NS	-0.428	-0.592
Hmamouchi, 2013[10]	70	40.0 ± 12.0	100	-0.32	NS	NS
	573	**38.9**[b]	**82.4%**[b]			

AS, ankylosing spondylitis; BASDAI, bath ankylosing spondylitis index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Vit D, 25-hydroxyvitamin D; NS, no significant correlation

[a]Standard deviation not reported

[b]Weighted average

Table 2 – Vitamin D, ESR, and CRP levels in patients with ankylosing spondylitis versus healthy controls

Author	Patients	Male (%)	Vit D	ESR	CRP
Lange, 2005[4]	58 EA	65.5	19.1 ± 9.8*	20.3 ± 11.9*	13.2 ± 8.0*
	vs. 58 C	65.5	29 ± 7	7 ± 4	-
Lange, 2001[5]	70 EA	68.6	22.0 ± 1	23 ± 17*	16 ± 13*
	vs. 45 C	-	24 ± 11	7 ± 4	-
Mermerci, 2010[6]	100 EA	75.0	21.7 ± 12.2*	26.3 ± 20.5*	21.4 ± 19.9*
	vs. 58 C	79.3	32.7 ± 8.8	7.5 ± 6.1	3.6 ± 1.7
Durmus, 2012[8]	99 EA	84.8	26.8 ± 11.7*	39.1 ± 28.5*	21.3 ± 25.5*
	vs. 42 C	78.6	31.1 ± 15.5	7.5 ± 6.3	4.1 ± 2.0
Erten, 2013[9]	48 EA	79.2	19.9 ± 9.5 *,a	32.6 ± 23.9	22.8 ± 18
	vs. 92 C	69.6	28.4 ± 15.2[a]	-	-
Hmamouchi, 2013[10]	70 EA	100	17.5 ± 9.7*	16.7 ± 2.5*,a	24.1 ± 19.6*
	vs. 140 C	100	21.9 ± 7.7	7.3 ± 6.4[a]	1.6 ± 1.2
Yazmalar, 2013[11]	72 EA	76.4	30.2 ± 26.7[b]	16.1 ± 14.1*	14.1 ± 16.8*
	vs. 70 C	62.9	30.3 ± 18.9[b]	7.8 ± 7.1	3.3 ± 0.8
Franck, 1993[12]	38 EA	65.8	21.6 ± 13.5	-	-
	vs. 52 C	55.8	20.1 ± 3.2	-	-
	555 EA	**78.0%[c]**	**22.8 ± 14.1[c]**		
	vs. 557 C	**-**	**26.6 ± 12.5[c]**		

AS, ankylosing spondylitis; C, control; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Vit D, 25-hydroxyvitamin D
*Significant difference reported by authors
[a]Unpublished data
[b]Averaged over winter and summer data
[c]Weighted average

D (<20 ng/mL) are present in a significant percentage of patients with autoimmune diseases such as diabetes mellitus type 1,[19] systemic lupus erythematosus and rheumatoid arthritis (RA).[20] As pointed out by Welsh et al.[21] in a review of vitamin D levels and RA, the cross-sectional studies included in this analysis are limited as they cannot rule out reverse causality. Thus, with the existing studies it is not possible to ascertain whether vitamin D deficiency is a cause, or a consequence, of AS.

Tumor necrosis factor alpha (TNF-α) is thought to play a role in chronic inflammation, and it is known to inhibit the binding of the vitamin D receptor to vitamin D responsive element (VDRE) of the osteocalcin gene. It may down-regulate the 24-hydroxylase activity in kidneys, possibly reducing vitamin D levels.[8] There has been some suggestion in the literature that vitamin D, as with other circulating vitamins, may be subject to an inverse acute phase response.[22] In other words, systemic inflammation may lower circulating levels of vitamin D.

On the other hand, vitamin D has been reported to inhibit expression of TNF-α,[23] and it follows that vitamin D deficiency may accelerate inflammation. Lange et al. noted a negative correlation between vitamin D levels and TNF-α in patients with AS.[4] Prospective studies suggest vitamin D deficiency is associated with an increased risk of RA development.[24] Well-designed prospective studies are required to determine whether vitamin D status has any relationship to the development of AS.

There are several possible explanations of the heterogeneity in the results. The studies used in this analysis had different sizes and statistical powers, and varied in their control of confounding factors. All these studies reported exclusion of patients with chronic and systemic diseases, but use of glucocorticoids, biological agents, bisphosphonates, and vitamin D supplementation itself was not controlled in all of them. The studies had differing percentages of male and female patients, and seasonality was not controlled in of those. Yazmalar et al. have found that although circulating levels of 25(OH) vitamin D do not vary significantly over the seasons, BASDAI scores are higher in winter months.[11] It is also known that circulating vitamin D levels are affected by body mass index, skin pigmentation, latitude, clothing and sunscreen use,[25] and it is not clear whether all of these studies controlled for these confounders.

Conclusion

In conclusion, patients with AS, as in other autoimmune diseases, appear to have lower vitamin D levels than healthy controls, however the cause is unclear. In studies to date, there has been no consistent link between vitamin D levels and disease activity in AS, neither evidence at this point that would justify the use of serum 25-hydroxyvitamin D_3 levels as a marker of disease activity. It remains to be seen whether vitamin D deficiency can predispose to the development of AS and if maintenance of optimal vitamin D levels can improve outcomes in AS.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Qubti MA, Flynn JA. Chapter 17. Ankylosing Spondylitis & the Arthritis of Inflammatory Bowel Disease. In: Imboden JB,

Hellmann DB, Stone JH, eds. Current Diagnosis & Treatment: Rheumatology. 3rd ed. New York: McGraw-Hill; 2013.
2. Bikle DD. What is new in vitamin D: 2006-2007. Curr Opin Rheumatol. 2007 Jul;19:383-8.
3. Gatenby P, Lucas R, Swaminathan A. Vitamin D deficiency and risk for rheumatic diseases: an update. Curr Opin Rheumatol. 2013 Mar;25:184-91.
4. Lange U, Teichmann J, Strunk J, Müller-Ladner U, Schmidt KL. Association of 1.25 vitamin D3 deficiency, disease activity and low bone mass in ankylosing spondylitis. Osteoporos Int. 2005;16:1999-2004.
5. Lange U, Jung O, Teichmann J, Neeck G. Relationship between disease activity and serum levels of vitamin D metabolites and parathyroid hormone in ankylosing spondylitis. Osteoporos Int. 2001 Dec;12:1031-5.
6. Mermerci Başkan B, Pekin Doğan Y, Sivas F, Bodur H, Ozoran K. The relation between osteoporosis and vitamin D levels and disease activity in ankylosing spondylitis. Rheumatol Int. 2010;30:375-81.
7. Arends S, Spoorenberg A, Bruyn GA, Houtman PM, Leijsma MK, Kallenberg CG et al. The relation between bone mineral density, bone turnover markers, and vitamin D status in ankylosing spondylitis patients with active disease: a cross-sectional analysis. Osteoporos Int. 2011;22:1431-9.
8. Durmus B, Altay Z, Baysal O, Ersoy Y. Does vitamin D affect disease severity in patients with ankylosing spondylitis? Chin Med J (Engl). 2012 Jul;125:2511-5.
9. Erten S, Kucuksahin O, Sahin A, Altunoglu A, Akyol M, Koca C. Decreased plasma vitamin D levels in patients with undifferentiated spondyloarthritis and ankylosing spondylitis. Intern Med. 2013;52:339-44.
10. Hmamouchi I, Allali F, El Handaoui B, Amine H, Rostom S, Abouqal R. The relation between disease activity, vitamin D levels and bone mineral density in men patients with ankylosing spondylitis. Rheumatol Rep. 2013;5:7-11.
11. Yazmalar L, Ediz L, Alpayci M, Hiz O, Toprak M, Tekeoglu I. Seasonal disease activity and serum vitamin D levels in rheumatoid arthritis, ankylosing spondylitis and osteoarthritis. Afr Health Sci. 2013 Mar;13:47-55.
12. Franck H, Keck E. Serum osteocalcin and vitamin D metabolites in patients with ankylosing spondylitis. Ann Rheum Dis. 1993;52:343-6.
13. Overbergh L, Decallonne B, Valckx D, Verstuyf A, Depovere J, Laureys J et al. Identification and immune regulation of 25-hydroxyvitamin D-1-alpha-hydroxylase in murine macrophages. Clin Exp Immunol. 2000;120:139-46.
14. Cutolo M, Pizzorni C, Sulli A. Vitamin D endocrine system involvement in autoimmune rheumatic diseases. Autoimmun Rev. 2011;11:84-7.
15. Chen CH, Yu DT, Chou CT. Biomarkers in spondyloarthropathies. Adv Exp Med Biol. 2009;649:122-32.
16. Hakkou J, Rostom S, Aissaoui N, Berrada Ghezioul K, Bahiri R, Abouqal R et al. Comparison of the BASDAI and the miniBASDAI in assessing disease activity in patients with ankylosing spondylitis. Clin Rheumatol. 2012 Mar;31:441-5.
17. Holick MF. Vitamin D deficiency. N Engl J Med. 2007 Jul 19;357:266-81.
18. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP et al. Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul;96:1911-30.
19. Mathieu C, Gysemans C, Giulietti A, Bouillon R. Vitamin D and diabetes. Diabetologia. 2005;48:1247-57.
20. Cutolo M, Otsa K, Paolino S, Yprus M, Veldi T, Seriolo B. Vitamin D involvement in rheumatoid arthritis and systemic lupus erythaematosus. Ann Rheum Dis. 2009;68:446-7.
21. Welsh P, Peters MJ, Sattar N. Is vitamin D in rheumatoid arthritis a magic bullet or a mirage? The need to improve the evidence base prior to calls for supplementation. Arthritis Rheum. 2011;63:1763-9.
22. Reid D, Knox S, Talwar D, O'Reilly DJ, Blackwell S, Kinsella J *et al*. Acute changes in the systemic inflammatory response is associated with transient decreases in circulating 25-hydroxyvitamin D concentrations following elective knee arthoplasty. Ann Clin Biochem. 2010;47:95-6.
23. Shany S, Levy Y, Lahav-Cohen M. The effects of 1alpha,24(S)-dihydroxyvitamin D(2) analog on cancer cell proliferation and cytokine expression. Steroids. 2001 Mar-May;66:319-25.
24. Song GG, Bae SC, Lee YH. Association between vitamin D intake and the risk of rheumatoid arthritis: a meta-analysis. Clin Rheumatol. 2012;31:1733-9.
25. Tsiaras WG, Weinstock MA. Factors influencing vitamin D status. Acta Derm Venereol. 2011 Mar;91:115-24.