Vitamin D Replacement Therapy: A Promising Adjunct in Cardiovascular Risk Management Among Patients with Rheumatoid Arthritis?

PATRICK H. DESSEIN

1. Sign up for our monthly e-table of contents
   http://www.jrheum.org/cgi/alerts/etoc

2. Information on Subscriptions
   http://jrheum.com/subscribe.html

3. Have us contact your library about access options
   Refer_your_library@jrheum.com

4. Information on permissions/orders of reprints
   http://jrheum.com/reprints.html

The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.

Vitamin D Replacement Therapy: A Promising Adjunct in Cardiovascular Risk Management Among Patients with Rheumatoid Arthritis?

Vitamin D is a steroid hormone that is best known for its central role in calcium and phosphate homeostasis[1,2,3]. Vitamin D deficiency [serum 25 OH-hydroxyvitamin D (25(OH)D) < 20 ng/ml] is complicated by rickets in children and osteomalacia in adults. Further, vitamin D deficiency and insufficiency [serum 25(OH)D < 30 ng/ml] contribute to osteoporosis and osteoporotic fractures through reduced bone mineral density and muscle mass, strength, and function, thus increasing the risk of falls. In persons 65 years of age or older, adequate vitamin D supplementation reduces the risk of hip and any nonvertebral fracture by 30% and 14%, respectively[2]. Impaired vitamin D status is prevalent worldwide, and vitamin D concentrations may have fallen further by 20% over the past 10 years[3].

The past 10 years have also witnessed a dramatically increased interest in vitamin D metabolism. This is because impaired vitamin D status was found to have — aside from its classical role in bone disease — numerous additional nonclassical adverse effects[1,3,4,5]. Thus, the vitamin D receptor (VDR), which is a member of the nuclear receptor superfamily, and key activating enzyme 25-OH-1α hydroxylase (CYP27B1), which converts 25(OH)D to its active metabolite 1,25 (OH)2D3, were shown to be present in multiple cell types. By its local synthesis and regulation of the transcription of as much as ~ 3% of the human genome[4], vitamin D can mediate its nonclassical effects through autocrine and paracrine mechanisms. Congruently, impaired vitamin D status has now been linked to a wide range of chronic conditions that include cardiovascular disease (CVD), diabetes, and autoimmune disorders. How relevant could these findings be to patients with rheumatoid arthritis (RA)?

RA results in enhanced endothelial activation and atherosclerosis that translate into a markedly increased risk of CVD events[6,7]. The identification of potential determinants of enhanced atherogenesis in RA is currently the subject of intensive investigation: to date, high-grade systemic inflammation and corticosteroid therapy were found to induce adverse metabolic risk factor profiles including insulin resistance, a direct effect of inflammatory molecules on endothelial activation; and genetic factors were found to enhance CVD risk in this disease[6,7]. Consideration of only traditional risk factors results in a large underestimation of the proportion of patients with RA who are at high risk of CVD events evidenced by the presence of carotid artery plaque, and who will therefore need intensive CV risk management[7].

In the context of the increased CVD risk in RA, 2 at least partially interrelated nonclassical adverse effects of impaired vitamin D status are particularly relevant: accelerated atherogenesis and immune dysfunction[1,3,5].

Both mechanistic and clinical association studies indicate that impaired vitamin D status is complicated by enhanced CVD risk[8,9,10,11,12]. Indeed, reduced circulating vitamin D concentrations are implicated in the genesis of metabolic risk factors including hypertension, impaired insulin secretion and sensitivity (a crucial mechanism in the metabolic syndrome), diabetes and dyslipidemia, as well as endothelial dysfunction. Vitamin D-receptor-null mice experience high renin hypertension, cardiac hypertrophy, and increased thrombogenicity[4]. 1,25 (OH)2D3 can favorably influence insulin secretion by inducing transcriptional activation of the human insulin gene and regulating extracellular calcium and calcium flux into the beta cell; as well, it can influence insulin sensitivity by stimulating the expression of the insulin receptor[9]. Vitamin D was shown to enhance insulin responsiveness for glucose transport[9]. Vitamin D additionally downregulates activation of nuclear factor κB (NF-κB), an important regulator of genes encoding proinflammatory cytokines, including interleukin 6 (IL-6), IL-1, and tumor necrosis factor-α (TNF-α), which are implicated in insulin resistance[9]. Using a Mendelian randomization approach, Skaaby and colleagues[10] recently documented a relation of vitamin D concentrations with

elevated high-density lipoprotein cholesterol and low triglyceride levels. Vitamin D deficiency associates with inflammation-linked endothelial dysfunction that can be reduced by inhibition of NF-κB upon using oral salsate[11]. 1,25 (OH)2D3 decreases foam cell formation by reducing oxidized low-density lipoprotein cholesterol uptake[8]. Decreased vitamin D concentrations were shown to associate with metabolic risk factors and predict CVD event rates[8,9,10,12]. Adequately designed randomized controlled trials that assess the influence of vitamin D on CVD events as the primary outcome are ongoing.

Secretion of 1,25 (OH)2D3 by immune cells is regulated by inflammatory molecules rather than calcemic stimuli, as applies to cells that participate in the classical effects of vitamin D[1]. 1,25 (OH)2D3 enhances the innate antibacterial defense of macrophages by promoting the secretion of bactericidal products including cathelicidin[1,3]. On the other hand, and with regard to adaptive immune responses, vitamin D downregulates not only antigen-presenting cells, thereby shifting T cell polarization from inflammatory Th1 to protective Th2, but also regulatory T cell phenotypes, which participate strongly in maintaining self-tolerance to autoantigens by suppressing autoreactive leukocytes and additionally reduce atherogenesis[13]. 1,25 (OH)2D3 also directly inhibits Th1 and Th17 cytokines and upregulates Th2 cytokines. Importantly, apart from its role in defending extracellular pathogens, IL-17 is a proinflammatory cytokine that contributes not only to the pathophysiology of autoimmune diseases including RA, but also activates a variety of leukocytes to produce cytokines, chemokines, reactive oxygen species, and matrix metalloproteinases that participate in the development of atherosclerosis and its complications[13]. Taken together, impaired vitamin D status is expected to result in immunological effects that increase not only the risk and disease severity of developing autoimmune diseases, but also accelerated atherogenesis.

In a recently reported investigation, Marder and colleagues[14] showed that in 50 patients with longstanding RA taking biologic agents with or without concomitant conventional disease-modifying agents (DMARD) or/and corticosteroids, IL-17 concentrations were associated with reduced microvascular function as assessed by the reactive hyperemia index, as well as increased pulse wave velocity, independent of traditional and other nontraditional CVD risk factors. These results indicate that IL-17 may indeed importantly contribute to the enhanced atherogenesis in RA.

In this issue of *The Journal*, the same investigators examined the potential effect of impaired vitamin D status on IL-17 production and atherogenesis among 87 patients with established RA taking biologic agents or/and conventional DMARD and corticosteroids[15]. About two-thirds (68%) had reduced vitamin D concentrations, and 42% of these were vitamin D deficient. In all patients and those with impaired vitamin D status, vitamin D concentrations

associated inversely with those of IL-17, independent of potentially important confounders. In the subgroup that was vitamin D deficient, vitamin D concentrations were also independently associated with enhanced microvascular function. These findings support the notion that impaired vitamin D status could be involved in both high-grade systemic inflammation and enhanced CVD risk in RA. As alluded to by the authors, 3 other recent investigations revealed that impaired vitamin D status in RA is also independently associated with metabolic risk factors including insulin resistance, and endothelial activation.

Both RA disease itself and the glucocorticoid therapy often used in the disease increase the risk of osteoporosis[16]. Further, VDR gene *FokI* polymorphisms of the B allele associate with RA incidence[17,18], and in a recent metaanalysis, low vitamin D intake was associated with RA incidence, and low vitamin D concentrations with RA activity[19]. Such findings prompted an international panel of 25 experts from various fields to include RA among a range of diseases in which assessment of vitamin D status and vitamin D supplementation targeted to reach levels of at least 30 to 40 but not more than 100 ng/ml is strongly recommended[5]. Interestingly also, combining 1,25 (OH)2D3 and TNF-α blockade was shown to have a significant additive effect, compared with single treatment, in controlling Th17-mediated synovial inflammation[20]. Whether vitamin D supplementation has a similar permissive effect in CVD risk management among patients with RA deserves further study. Conceptually, reduced vitamin D concentrations in active RA could reflect a negative acute phase response and thereby be partially or fully explained by the process of reverse causality. However, findings of recent investigations do not substantiate this possibility[21,22].

Appropriate vitamin D supplementation is easy to administer, nontoxic, and inexpensive[5]. Whether vitamin D supplementation can contribute to improved disease outcomes such as reduced disease activity and improved CVD event rates in RA requires confirmation in randomized controlled trials. However, evidence reported to date suggests that withholding vitamin replacement is not advisable. For the treating physician, it may therefore be prudent, if not ethically indicated, to routinely monitor and manage impaired vitamin D status in patients with autoimmune diseases, including those with RA.

PATRICK H. DESSEIN, MD, FCP(SA), FRCP(UK), PhD,
Cardiovascular Pathophysiology and Genomics Research Unit,
School of Physiology, Faculty of Health Sciences,
University of the Witwatersrand,
Johannesburg, South Africa.

Address correspondence to Professor Patrick H. Dessein, P.O. Box 1012, Melville 2109, Johannesburg, South Africa. E-mail: Dessein@telkomsa.net

REFERENCES

1. Verstuyf A, Carmeliet G, Bouillon R, Mathieu C. Vitamin D: a pleiotropic hormone. Kidney Int 2010;78:140-5.
2. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med 2012;367:40-9.
3. Hewison M. Vitamin D and the immune system: new perspectives on an old theme. Endocrinol Metab Clin North Am 2010;39:365-79.
4. Bouillon R, Carmellet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev 2008;29:726-76.
5. Souberbielle J-C, Body J-J, Lappe JM, Plebani M, Shoenfeld Y, Wang TJ, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice. Autoimmun Rev 2010;9:709-15.
6. Dessein PH, Joffe BI. When is a patient with rheumatoid arthritis at risk for cardiovascular disease? J Rheumatol 2006;33:201-3.
7. Corrales A, Gonzalez-Juanatey C, Peiro ME, Blanco R, Llorca J, Gonzalez-Gay MA. Carotid ultrasound is useful for the cardiovascular risk stratification of patients with rheumatoid arthritis: results of a population-based study. Ann Rheum Dis 2013 Mar 16. [E-pub ahead of print]
8. Ferder M, Inserra F, Manucha W, Ferder L. The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the rennin-angiotensin system. Am J Physiol 2013;304:C1027-39.
9. Pittas AG, Lau J, Hu F, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 2007;92:2017-29.
10. Skaaby T, Husemoen LL, Martinussen T, Thyssen JP, Melgaard M, Thuesen BH, et al. Vitamin D status, filaggrin genotype, and cardiovascular risk factors: a Mendelian randomization approach. PLoS One 2013;8:e57647.
11. Jablonski KL, Chonchol M, Pierce GL, Walker AE, Seals DR. 25-Hydroxyvitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction in middle-aged and older adults. Hypertension 2011;57:63-9.
12. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503-11.
13. Butcher M, Galkina E. Current view on the functions of IL-17-producing cells in atherosclerosis. Thromb Haemost 2011;106:787-95.
14. Marder W, Khalatbari S, Myles JD, Hench R, Yalavarthi S, Lustig S, et al. Interleukin 17 as a novel predictor of vascular function in rheumatoid arthritis. Ann Rheum Dis 2011;70:1550-5.
15. Ranganathan P, Khalatbari S, Yalavarthi S, Marder W, Brook R, Kaplan MJ. Vitamin D deficiency, interleukin 17, and vascular function in rheumatoid arthritis. J Rheumatol 2013;40:1529.
16. Baschant U, Lane NE, Tuckermann J. The multiple facets of glucocorticoid action in rheumatoid arthritis. Nat Rev Rheumatol 2012;8:645-55.
17. Lee YH, Bae SC, Choi SJ, Ji JD, Song GG. Associations between vitamin D receptor polymorphisms and susceptibility to rheumatoid arthritis and systemic lupus erythematosus: a meta-analysis. Mol Biol Rep 2011;38:3643-51.
18. Hitchon CA, Sun Y, Robinson DB, Peschken CA, Bernstein CN, Siminovitch KA, et al. Vitamin D receptor polymorphism rs2228570 (Fok 1) is associated with rheumatoid arthritis in North American natives. J Rheumatol 2012;39:1792-7.
19. Song GG, Bae S-C. Association between vitamin D intake and the risk of rheumatoid arthritis: a meta-analysis. Clin Rheumatol 2012;31:1733-9.
20. van Hamburg JP, Asmawidjaja PS, Davelaar N, Mus AM, Cornelissen F, van Leeuwen JP, et al. TNF blockade requires 1,25(OH)2D3 to control human Th17-mediated synovial inflammation. Ann Rheum Dis 2012;71:606-12.
21. Hasan E, Olusi S, Al-Awadhi A, Mokaddem K, Sharma P, George S. Effects of rituximab treatment on the serum concentrations of vitamin D and interleukins 2, 6, 7, and 10 in patients with rheumatoid arthritis. Biologics 2012;6:31-5.
22. Welsh P, Peters MJ, McInnes IB, Lems WF, Lips PT, McKellar G, et al. Vitamin D deficiency is common in patients with RA and linked to disease activity, but circulating levels are unaffected by TNFα blockade: results from a prospective cohort study. Ann Rheum Dis 2011;70:1165-7.