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Relationship Between Vitamin D and Rheumatoid Arthritis Disease

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Abstract: Rheumatoid arthritis is a chronic inflammatory disease in which the synovial membrane of the joint becomes inflamed, resulting in a swelling, stiffness, pain, limited range of motion, joint deformity and disability. Vitamin D is the "sunshine vitamin" which is converted in the body to a hormone 1, 25-dihydroxyvitamin D_3 by the photolytic action of ultraviolet light on the skin. Vitamin D plays an important role, along with the essential minerals calcium and phosphorus, in the maintenance of healthy bones and teeth. An inverse association between vitamin D intake and rheumatoid arthritis was found in some prospective studies. Although vitamin D has been implicated in a decreased risk of autoimmune diseases such as type 1 diabetes and multiple sclerosis, its role in decreasing the risk of rheumatoid arthritis remains equivocal. This scientific review is written to illustrate the possible relationships between rheumatoid arthritis and vitamin D.

Key words: Rheumatoid arthritis, vitamin D, Vitamin D Receptors (VDR)

INTRODUCTION

Arthritic conditions encompass more than 100 different diseases and conditions affecting the joints, the tissues surrounding the joints and the connective tissue. Arthritic conditions are among the most common diseases in the world and include osteoarthritis, Rheumatoid Arthritis (RA) and gout (Rizzo, 2005). Arthritic conditions affect nearly one in sex North Americans and are the leading cause of disability among Americans 18 years of age and older (U.S. Department of Health and Human Services, 2001) and about 22% of U.S. adults have arthritis (ACR, 2010).

Common misconceptions about arthritic conditions are they only affect older persons, that they are an inevitable consequence of aging, they are diagnosed in people of all ages, including children and teens (Lee, 2007). Juvenile RA affects 70.000 to 100.000 children in US and is one of the most common chronic conditions of childhood (Rizzo, 2005). There are several factors known to increase the risk of arthritic conditions, three of which are modifiable: overweight, joint injuries and infections. Non-modifiable risk factors include female sex, age and family history (Rizzo, 2005).

RA is an autoimmune disease, in which a person's immune system attacks his or her own healthy tissues (Lee, 2007). RA is the most common inflammatory arthritis across the world. Although the etiology of RA remains a mystery, a variety of studies suggest that a blend of environmental and genetic factors are responsible and both affecting the prevalence of autoimmune disease (Turhanoglu *et al*., 2010).

Vitamin D is the "sunshine vitamin" which is converted in the body to a hormone 1, 25-dihydroxyvitamin D_3 by the photolytic action of ultraviolet light on the skin. Vitamin D plays an important role, along with the essential minerals calcium and phosphorus, in the maintenance of healthy bones and teeth (Combs, 1988). Moreover vitamin D sufficiency, especially during the childhood and adolescent years, is critically important not only for bone health, but also for the prevention of many serious chronic diseases, including cancer, cardiovascular heart disease and autoimmune diseases. It has been suggested that vitamin D deficiency during infancy and childhood may imprint an increased risk of these chronic diseases for the rest of one's life (Holick, 2006).

An inverse association between vitamin D intake and RA was found in the prospective cohort study done by the Iowa Women's Health Study (Merlino *et al*., 2004). Vitamin D is a hormone essential for bone and mineral homeostasis and is also involved in the regulation of cells in the innate and adaptive immune system through the Vitamin D Receptor (VDR) as a suppressor of pro-inflammatory responses (Mathieu *et al*., 2001). Although vitamin D has been implicated in a decreased risk of autoimmune diseases such as type 1 diabetes and multiple sclerosis, its role in decreasing the risk of RA remains equivocal (Hypponen *et al*., 2001; Holick, 2007). The aim of this review is to summarize the currently available information for the effect of vitamin D on RA disease.

Rheumatoid arthritis

Introduction: The name (RA) is based on the term" rheumatic fever", an illness which includes joint pain and is derived from the Greek word *rheumatos* ("flowing"). The suffix-oid ("resembling") gives the translation as joint inflammation that resembles rheumatic fever. The first recognized description of rheumatoid arthritis was made in 1800 by Dr. Augustin Jacob Landré-Beauvais (1772-1840) of Paris (Landre-Beauvais, 2001).

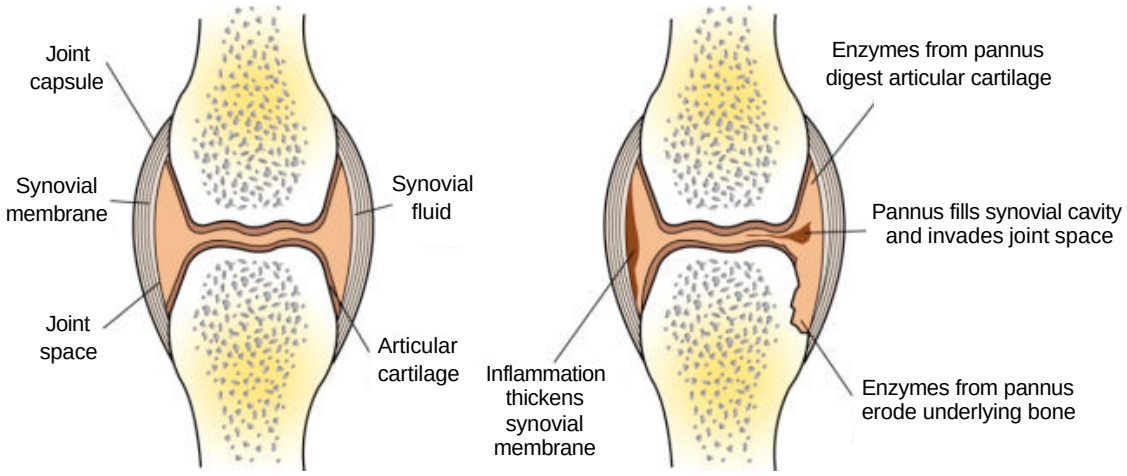

Fig. 1: Pathophysiology of RA (A normal joint at left and a joint affected by rheumatoid arthritis right)

Rheumatoid arthritis is a chronic inflammatory disease in which the synovial membrane of the joint becomes inflamed, resulting in a swelling, stiffness, pain, limited range of motion, joint deformity and disability (Lipsky, 2005). RA affects approximately 0.8% of the population, is more common in older persons and affects female three times more often than males (Pattison *et al*., 2004).

Although RA primarily affects the joints, it also can affect other tissues, resulting in anorexia, weight loss, fatigue, general itching and stiffness (Lee, 2007). Extra-articular ("outside the joints") manifestations occur in about 15% of individuals with rheumatoid arthritis. It can be difficult to determine whether disease manifestations are directly caused by the rheumatoid process itself, or from side effects of the medications commonly used to treat it-for example, lung fibrosis from methotrexate, or osteoporosis from corticosteroids (Turesson *et al*., 2003).

Pathophysiology: Rheumatoid arthritis is an autoimmune disease, the cause for which is still unknown. It is a systemic (whole body) disorder principally affecting synovial joints. As shown in Fig. 1, a normal joint (left) and a joint affected by rheumatoid arthritis (right) are compared. Early changes shown on the left side of the affected joint include inflammation and thickening of the synovial membrane. Late changes shown on the right side of the affected joint include development of pannus, erosion of articular cartilage and bone and filling of the joint space by pannus (Lee, 2007).

As with most autoimmune diseases, it is important to distinguish between the causes that trigger the inflammatory process and those that permit it to persist and progress. Chemical mediators (Cytokines) give rise to inflammation of joint synovium. Constitutional symptoms such as fever, malaise, loss of appetite and weight loss are also due to cytokines released in to the blood stream. Blood vessel inflammation (vasculitis) affecting many other organ systems can give rise to systemic complications (Choy and Panayi, 2001).

It has long been suspected that certain infections could be triggers for this disease. The "mistaken identity" theory suggests that an infection triggers an immune response, leaving behind antibodies that should be specific to that organism. The antibodies are not sufficiently specific, though and set off an immune attack against part of the host. Because the normal host molecule "looks like" a molecule on the offending organism that triggered the initial immune reaction-this phenomenon is called molecular mimicry. Some infectious organisms suspected of triggering rheumatoid arthritis include *Mycoplasma*, *Erysipelothrix*, parvovirus B19 and rubella, but these associations have never been supported in epidemiological studies. Nor has convincing evidence been presented for other types of triggers such as food allergies. There is also no clear evidence that physical and emotional effects, stress and improper diet could be a trigger for the disease. The many negative findings suggest that either the trigger varies, or that it might in fact be a chance event (Edwards *et al*., 1999).

Epidemiological studies have confirmed a potential association between RA and two herpesvirus infections: Epstein-Barr Virus (EBV) and Human Herpes Virus 6 (HHV-6) (Alvarez-Lafuente *et al*., 2005). Individuals with RA are more likely to exhibit an abnormal immune response to the Epstein-Barr virus (Ferrell *et al*., 1981; Catalano *et al*., 1979). The allele HLA-DRB1*0404 is associated with low frequencies of T cells specific for the EBV glycoprotein 110 and predisposes one to develop RA (Balandraud and Roudier, 2004).

The factors that allow the inflammation, once initiated, to become permanent and chronic, are much more clearly understood. The genetic association with HLA-DR4 is believed to play a major role in this, as well as the newly discovered associations with the gene PTPN22 and with two additional genes, all involved in regulating immune responses (Plenge *et al*., 2007). It has also become clear from recent studies that these genetic factors may interact with the most clearly defined environmental risk factor for rheumatoid arthritis, namely cigarette smoking (Padyukov *et al*., 2004).

Diagnosis: When RA is being clinically suspected, immunological studies are required, such as Rheumatoid Factor (RF, a specific antibody). A negative RF does not rule out RA; rather, the arthritis is called *seronegative*. During the first year of illness, RF is frequently negative. 80% of individuals eventually convert to seropositive status. RF is also seen in other illnesses, like Sjogren's syndrome and in approximately 10% of the healthy population, therefore the test is not very specific (American Association for Clinical Chemistry, 2006).

Because of this low specificity, a new serological test has been developed in recent years, which tests for the presence of so called Anti-Citrullinated Protein Antibodies (ACPA) (American Association for Clinical Chemistry, 2005). Like RF, this test can detect approximately 80% of all RA cases, but is rarely positive if RA is not present, giving it a specificity of around 98%. In addition, ACP antibodies sometimes can be detected in early stages of the disease, or even before onset of clinical disease. Currently, the most common test for ACP antibodies is the anti-CCP (cyclic citrullinated peptide) test (American Association for Clinical Chemistry, 2005). Also, several other blood tests are usually done to discriminate for other causes of arthritis, such as lupus erythematosus. The Erythrocyte Sedimentation Rate (ESR), C-reactive protein, full blood count, renal function, liver enzymes and other immunological tests (e.g. antinuclear antibody/ANA) (American Association for Clinical Chemistry, 2004).

Disease activity can be assessed according to the Disease Activity Score including 28 joint counts (DAS28). Three components of DAS28 test are included: erythrocyte sedimentation rate, patient-assessed global score (0-100) and swollen and tender joint counts (both 0-28). High activity of the disease will be defined as a DAS28>5.1, moderate activity of disease will be defined as a 3.2<DAS28<5.1 and low activity of disease will be defined as a DAS28<3.2 (Lee, 2007).

Classification criteria: The American College of Rheumatology (ACR) in 1987 (ACR; formerly, the American Rheumatism Association [ARA]) has defined the following criteria for the classification of rheumatoid arthritis:

- Morning stiffness of more than 1 hr most mornings for at least 6 weeks.
- Arthritis and soft-tissue swelling of >3 of 14 joints/joint groups, present for at least 6 weeks
- Arthritis of hand joints, present for at least 6 weeks
- Symmetric arthritis, present for at least 6 weeks
- Subcutaneous nodules in specific places
- Rheumatoid factor at a level above the 95th percentile
- Radiological changes suggestive of joint erosion

At least four criteria have to be met for classification as RA (Arnett *et al*., 1981).

A joint working group from the ACR and the European League Against Rheumatism (ACR/EULAR) developed a new approach to classifying RA. The work focused on identifying, among patients newly presenting with undifferentiated inflammatory synovitis, factors that best discriminated between those who were and those who were not at high risk for persistent and/or erosive disease. This new classification system redefines the current paradigm of RA by focusing on features at earlier stages of disease that are associated with persistent and/or erosive disease, rather than defining the disease by its late-stage features (Aletaha *et al*., 2010).

In the new criteria set as shown in Table 1, classification as “definite RA” is based on the confirmed presence of synovitis in at least 1 joint, absence of an alternative diagnosis that better explains the synovitis and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in 4 domains: number and site of involved joints (score range 0-5), serologic abnormality (score range 0-3), elevated acute-phase response (score range 0-1) and symptom duration (2 levels; range 0-1) (Aletaha *et al*., 2010).

Treatment: There is no known cure for rheumatoid arthritis. However, many different types of treatment can be used to alleviate symptoms and/or to modify the disease process. The goal of treatment in this chronic disease must be for dual purposes: to alleviate the current symptoms and to prevent the future destruction of the joints and resulting handicap if the disease is left unchecked. These two goals may not always coincide, while pain relievers may achieve the first goal, they do not have any impact on the long-term consequences. For these reasons, most authorities believe that most RA should be treated by at least one specific anti-rheumatic medication to which other medications and non-medical interventions can be added as needed (O'Dell, 2004).

Pharmacological treatment: Pharmacological treatment of RA can be divided into Disease-Modifying Antirheumatic Drugs (DMARDs), anti-inflammatory agents and analgesics. Anti-inflammatories and analgesics improve pain and stiffness but do not prevent

Table 1: The 2010 American college of rheumatology/european league against rheumatism classification criteria for rheumatoid arthritis by Aletaha *et al*. (2010)

	Score
Target population (Who should be tested?): Patients who	
1) Have at least 1 joint with definite clinical synovitis (swelling)	
2) With the synovitis not better explained by another disease	
Classification criteria for RA (score-base algorithm: add score categories (A-D);	
a score of ≥6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvement	0
1 large joint	1
2-10 large joints	2
1-3 small joints (with or without involvement of large joints)	3
4-10 small joints (with or without involvement of large joints)	4
≥10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and Negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	0
Normal CRP and normal ESR	1
Abnormal CRP or abnormal ESR	
D. Duration of symptoms	0
<6 weeks	1
≥6 weeks	

joint damage or slow the disease progression. Anti-inflammatory agents used in RA treatment include glucocorticoids and Non-Steroidal Anti-Inflammatory Drug (NSAIDs) and analgesics include acetaminophen, opiates, diproqualone and lidocaine topical (Hasler, 2006).

DMARDs have been found to produce durable remissions and delay or halt disease progression. In particular they prevent bone and joint damage from occurring secondary to the uncontrolled inflammation. This is important as such damage is usually irreversible (O'Dell, 2004).

There may be other reasons why starting DMARDs early is beneficial as well as prevention of structural joint damage. In the early stage of the disease, the joints are increasingly infiltrated by cells of the immune system that signal to one another and are thought to set up self-perpetuating chronic inflammation. Interrupting this process as early as possible with an effective DMARD (such as methotrexate) appears to improve the outcome of RA for years afterwards. Delaying therapy for as little as few months after the onset of symptoms can result in worse outcomes in the long term. There is therefore considerable interest in establishing the most effective therapy with early arthritis, when they are most responsive to therapy and have the most to gain (Vital and Emery, 2005).

Dietary treatment: There is evidence that lower intakes of vegetables, fruits and dietary sources of vitamin C are associated with increased risk of developing RA (Rennie *et al*., 2003). However, a research by Canter and his colleague at 2007 which they concluded that there is presently no convincing evidence that selenium, vitamin A, or vitamin C are effective in the treatment of any type of arthritis (Canter *et al*., 2007). Other researchers have been observed that there is a lower risk of developing RA in countries such as Italy and Greece, where oil-rich fish, olive oil, vegetables and fruits are consumed in greater amounts compared to other countries have a higher risk of developing RA (Rennie *et al*., 2003).

Omega-3 fatty acids (eicosapentaenoic acid; EPA and docosahexaenoic acid; DHA) consumption from fish oil and other sources reduce the synthesis of chemicals known to stimulate joints inflammation and cartilage degradation with lesser need to take NSAIDs to relieve pain (Volker *et al*., 2000; Cleland *et al*., 2003). On the other hand, a diet low in arachidonic acid (omega-6 fatty acids) ameliorates clinical signs of inflammation in patients with RA (Adam *et al*., 2003). Gamma-Linolenic Acid (GLA) is an omega-6 fatty acid found in oils of some plant seeds and cow milk. There is some preliminary evidence conducted by Little and Parsons in 2000 that GLA may be beneficial for RA. In the body, GLA can be converted into substances that reduce inflammation (Little and Parsons, 2000).

Research on other supplements and herbs for RA symptoms is still in the early stages. Thunder god vine (Tripterygium wilfordii) has been used for centuries in traditional Chinese medicine. Extracts are prepared from the skinned root of the herb, as other parts of the plant are highly poisonous (Tao *et al*., 2002). Findings from laboratory and animal studies suggest that thunder god vine may fight inflammation and suppress the immune system. In small clinical trials involving people with RA thunder god vine extracts appeared to provide some relief of symptoms (Canter *et al*., 2006). Thunder god vine can cause severe side effects that can cause

diarrhea, stomach upset, hair loss, headache and skin rash. The herb can also affect the reproductive system, possibly causing menstrual changes in women and infertility in men. Long-term use of thunder god vine may decrease bone mineral density in women, potentially increasing the risk of osteoporosis (Tao *et al*., 2002). In animal studies, extracts of turmeric (Curcuma longa) containing the chemical curcumin were found to protect joints from inflammation and damage (Funk *et al*., 2006). Laboratory studies have identified anti-inflammatory compounds in ginger (*Zingiber officinale*) which is gingerol. It has been shown that gingerol is effective against cytokines synthesized and secreted at sites of inflammation (Lantz *et al*., 2007).

Citrus fruits, chocolate, alcohol, red meats, flour products, spices and fizzy drinks are often implicated in the aggravation of RA symptoms (Martin, 1998). Previous investigations have found that a period of fasting followed by a regimented vegetarian diet can decrease RA disease activity. This led to investigations into whether protein and red meat intake play a role in increasing risk of developing RA (Liao *et al*., 2009).

Vitamin D: Vitamin D deficiency has been a long-standing public health issue. This condition was first described in association with skeletal deformities by Glisson and his group during the mid-17th century in London, England. Despite numerous preventive strategies, vitamin D deficiency has remained a global health problem among children (Leanne *et al*., 2007).

The National Institution of Health (NIH) reported that serum concentration of 25-Hydroxyvitamin D3 [25 (OH) D_3] is the best indicator of the vitamin D status. It reflects vitamin D produced cutaneously and that obtained from food and supplements and has a fairly long circulating half life of 15 days. Different concentrations of serum 25 (OH) D_3 are associated with deficiency, adequacy for bone health and optimal overall health (Table 2) (NIH, 2008). Several factors potentially affect vitamin D status; these include genetic factors, adiposity and factors affecting the cutaneous synthesis of vitamin D such as skin pigmentation, age, season, latitude, melanin concentration, clothing and use of sunscreens (SACN, 2007).

It is clear that both genetic and environmental factors affect the prevalence of autoimmune diseases. Therefore, the fact that vitamin D has been implicated as a factor in several different autoimmune diseases suggests that vitamin D might be one of the environmental factors that among others normally participates in the control of self-tolerance (Arnson *et al*., 2007). It has been found that polymorphisms in the Vitamin D Receptors (VDR) have been correlated with increased susceptibility of RA (Garcia-Lozano *et al*., 2001; Maalej *et al*., 2005).

Rheumatoid arthritis and vitamin D: The discovery of VDR in the cells of the immune system and the fact that activated dendritic cells produce vitamin D hormone suggested that vitamin D could have immunoregulatory properties (Fritsche *et al*., 2003). VDR, a member of the nuclear hormone receptor superfamily, was identified in mononuclear cells, dendritic cells, antigen-presenting cells and activated T-B lymphocytes (Arnson *et al*., 2007).

A physiological role for vitamin D in the immune system is supported by the presence of the VDR in primary lymphoid organs. The primary lymphoid organs (bone marrow and thymus) are the centers where the immune system develops and differentiates (Deluca and Cantorna, 2001; Langub *et al*., 2000). As a matter of fact, both genetic and environmental factors contribute to the etiology of autoimmnune diseases. T cells (lymphocytes that differentiate in the thymus) have been shown to play fundamental roles in autoimmune diseases. Quiescent CD4 + T cells express VDRs at low concentrations, which increases five-fold after their activation (Mahon *et al*., 2003). The effects of vitamin D on the acquired, antigen-specific immune response, are characterized by inhibition of T-lymphocyte proliferation (Lemire, 1992), particularly of the Th1 arm (Th 1 is a subset of the T helper cells that secretes cytokines) (Mattner *et al*., 2000). Treatment of CD4 T cells with vitamin D inhibits Th1 cell proliferation and cytokine production (Boonstra *et al*., 2001; Van and Mathieu, 2005).

Addition of vitamin D was shown also to inhibit the expression of the Interleukin-6 (IL-6). IL-6 is an interleukin that acts as both a pro-inflammatory and anti-inflammatory cytokine (Stockinger, 2007). Interestingly, in B cells vitamin D has been shown to inhibit antibody secretion and autoantibody production (Linker-Israeli *et al*., 2001). *In vitro*, vitamin D inhibits the differentiation of monocytes into dendritic cells and interferes with the stimulatory activity that T cells exert on them (Griffin *et al*., 2001). It has been shown that vitamin D is one of the most efficient blockers of dendritic cell differentiation and

Table 2: Serum 25-Hydroxyvitamin D [25(OH) D] concentration and health by NIH (2008)*

Health status	nmol/L**	ng/ml**
Associated with vitamin D deficiency and rickets in infant and young children.	<27.5	<11
Generally considered inadequate for bone and overall health in healthy individuals.	<25-37.5	<10-15
Proposed by some as desirable for overall health and disease prevention.	≥75	≥30
Considered potentially toxic, leading to hypercalcemia and hyperphosphatemia.	Consistently>500	Consistently>200

*Serum concentration of 25 (OH) D are reported in both nanograms per milliliter (ng/ml) and nanomoles per liter (nmol/L).
**1 ng/ml = 2.5 nmol/L

of interleukin secretion. *In vitro* vitamin D stimulates phagocytosis and killing of bacteria by macrophages but suppresses the antigen-presenting capacity of these cells and of dendritic cells (Griffin *et al*., 2000). Vitamin D has been found to promote the induction of monocytic differentiation to macrophages and modulate macrophage responses, preventing them from releasing inflammatory cytokines and chemokines (Helming *et al*., 2005).

It has been observed that greater intake of vitamin D was associated with a lower risk of RA, as well as lower vitamin D was found associated with higher disease activity (Merlino *et al*., 2004). Since lower vitamin D serum levels have been also associated with higher RA disease activity, in a recent study were evaluated serum 25(OH)D3 levels in 64 female RA patients from north Europe (Estonia) and 54 RA patients from south Europe (Italy) during winter and summer and were correlated with the disease activity score (DAS28) (Cutolo *et al*., 2006).

In addition, there may be a higher vitamin D requirement for patients at risk for developing autoimmunity and for those that already have an autoimmune disease such as systemic lupus erythematosus (Kamen *et al*., 2006). In fact, the optimal amount of vitamin D to support the immune response may be different from the amount required to prevent vitamin D deficiency or to maintain calcium homeostasis (Rejnmark *et al*., 2004). One review suggest that the optimal plasma 25(OH)D3 concentration lies between 50-80 nmoles/L, other experts suggesting between 75-125 nmol/L (Chatfield *et al*., 2007).

Conclusion: Serum vitamin D levels have been found to correlate inversely with the RA disease activity. Greater intake of vitamin D was associated with a lower risk of RA, as well as a significant clinical improvement was strongly correlated with the immunomodulating potential in vitamin D-treated RA patients.

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