

**Original Review Article****The Correlation of Serum Vitamin D and HDL Level with Disease Activity Score -28 In Patients of Rheumatoid Arthritis**

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Dr Cankatika Choudhury**Abstract**

Rheumatoid arthritis (RA) is the most common chronic symmetric polyarthritis characterized by erosive arthritis, joint destruction and a variety of extraarticular manifestations. Insights gained by a wealth of basic and clinical research over the past two decades have revolutionized the contemporary paradigms for the diagnosis and management of RA. A clinical state defined as low disease activity or remission is the optimal goal of therapy. Composite indices, such as the Disease Activity Score -28 or DAS28 is very useful in practise. Vitamin D has an immunomodulatory role in RA and its reduced intake is associated with increased disease activity. High inflammatory burden in RA contributes to cardiovascular morbidity and there's reduced levels of High-Density Lipoprotein (HDL) cholesterol. Hence, Serum Vitamin D & HDL level can serve as useful markers of disease activity in RA.

Introduction

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory arthritis. Although most readily recognized by its articular manifestations, RA can affect any organ system. Whether disease expression is confined to mild articular manifestations or manifests as severe multisystem disease, our current understanding demands that patients receive early and aggressive therapy^[1]. Achieving prompt control of local and systemic inflammatory processes minimizes damage of articular structures, preserves function, prevents premature mortality, disability & compromised quality of life. Genetic,

environmental, hormonal, immunological & infectious factors may play significant roles. Reduced Vitamin D intake has been implicated in the pathogenesis of RA and also with increased disease activity in patients of RA^[1]. Vitamin D has emerged as a novel immunomodulator. It helps in the maintenance and regulation of immune homeostasis by potentiating the innate response but suppressing adaptive immunity^[2,3]. The most common cause of death in patients with RA is cardiovascular disease^[6]. Inflammation is associated with qualitative & quantitative changes in lipoproteins with the anti-inflammatory & atheroprotective roles associated with HDL

cholesterol significantly altered. RA therapies can also increase lipid levels which may reflect normalization of lipids due to their inflammatory-dampening effects^[7]. A clinical state defined as low disease activity or remission is the optimal goal of therapy measured by composite indices, such as the Disease Activity Score -28 or DAS28. The two novel biomarkers Vitamin D and HDL can be thus correlated with DAS 28 in clinical practise to understand the driving inflammatory burden and guide therapeutic decisions.

Landmarks In Rheumatoid Arthritis

A) Classification Criteria

In 2010, a collaborative effort between the American College of Rheumatology (ACR)

and the European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for RA in an effort to improve early diagnosis with the goal of identifying patients who would benefit from early introduction of disease-modifying therapy. Application of the newly revised criteria yields a score of 0–10, with a score of 6 fulfilling the requirements for definite RA^[4,5]. It is important to emphasize that the new 2010 ACR-EULAR criteria are "classification criteria" as opposed to "diagnostic criteria" and serve to distinguish patients at the onset of disease with a high likelihood of evolving into a chronic disease with persistent synovitis and joint damage.

Table 1: ACR EULAR 2010 Classification Criteria

		Score
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (MCP, PIP, Thumb IP, MTP, wrists)	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive anti-CCP antibodies (more than 3 times ULN)	2
	High-positive RF or high-positive anti-CCP antibodies (>3 times ULN)	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	Less than 6 weeks	0
	More than or 6 weeks	1

B) Drug Therapy

Several developments during the past two decades have changed the therapeutic landscape in RA^[8,9]. They include: (1) the emergence of Methotrexate as the disease-modifying antirheumatic drug (DMARD) of first choice for the treatment of early RA; (2)

the development of novel highly efficacious biologicals that can be used alone or in combination with methotrexate; and (3) the proven superiority of combination DMARD regimens over methotrexate alone^[10].

- **Disability and Remission Scales:** Complete remission has been stringently defined as the

total absence of all articular and extraarticular inflammation and immunologic activity related to RA. In an effort to standardize and simplify the definition of remission for clinical trials, the ACR and EULAR developed two provisional operational definitions of remission in RA. A patient may be considered in remission if he or she 1) meets all of the clinical and laboratory criteria listed as follows:

- Tender joint count 1
- Swollen joint count 1
- C-reactive protein 1 mg/dL
- Patient global assessment 1 (on a 0–10 scale)

OR

A composite Simplified Disease Activity Index (SDAI) score of <3.3.

The SDAI is calculated by taking the sum of a tender joint and swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale), and C-reactive protein (in mg/dl)^[11].

USE OF DAS -28: Originally developed for the purpose of standardizing & comparing results in clinical trials of new drugs for treating RA^[12]. In UK, a score of greater than 5.1 on two occasions are mandatory to be eligible for NHS funded treatment with biologics. DAS 28 should be measured every 6 months as a persistent fall by at least 1.2 points from pre-treatment score is required to allow continuation of treatment and can be calculated with either ESR or CRP [13].

- $DAS\ 28 = 0.56 \times \text{sq. rt (TJC28)} + 0.28 \times \text{sq. rt (SJC 28)} \times \log (\text{ESR}) + 0.014 \times \text{GH}$
- $DAS\ 28 - \text{CRP} = [0.56 \times \text{sq. rt (TJC28)} + 0.28 \times \text{sq. rt (SJC 28)} \times \log (\text{CRP} + 1)] + 0.014 \times \text{GH} + 0.96$

Changing Concepts in the Pathobiology of Rheumatoid Arthritis

RA is widely prevalent throughout the world. The overall worldwide prevalence is 0.8% and steadily increases to 5 % in women over the age of 70. RA is two to three times more common in women compared to men and the affected age group is 25-

55 years which is the working and productive cadre of the societal setup. In India, the prevalence is estimated to be 0.7% making it a very important area of research. Several developments during the past two decades have changed the therapeutic landscape in RA. Vitamin D has emerged as a novel immunomodulator. Vitamin D has modulating effects on B lymphocytes, Immunoglobulin (Ig) production and several cytokines [14]. Its role has been implicated in the causation & perpetuation of Systemic lupus erythematosus (SLE), Multiple sclerosis, inflammatory bowel diseases, psoriasis & active Bechet's disease^[15].

Role of Vitamin D in Immune Processes

The immune modulatory role of 1,25 (OH)₂ D is primarily due to local production of the hormone by macrophages, dendritic cells and activated lymphocytes. The expression of Vitamin D receptors on these cells (VDR) allows 1,25(OH)₂D to regulate expression of cytokine & cell receptors^[16].

Vitamin D metabolites regulate innate immunity by interacting with macrophages which express 1-hydroxylase the enzyme responsible for converting 25 (OH) D into the biologically active 1,25 (OH)₂D. macrophages recognize & respond to pathogen- associated molecular patterns (PAMPs). These PAMPs are recognized by pattern recognition receptors (PRRs) on the cell surface of macrophages of which an important group is Toll Like Receptors (TLRs). The most important Vitamin D associated immune response is the release of *cathelicidin* from macrophages in response to microbial proteins^[16,17].

Vitamin D also plays a significant role in adaptive immunity. Activated T & B lymphocytes respectively express VDR and therefore allow 1,25 (OH)₂D to suppress their proliferation & reduce Ig production. The primary target is Th1 helper cell which modulates cytokine production. Interleukin-12 produced by macrophages and DCs differentiates naïve the lymphocytes into Th1 lymphocytes & this action is blocked by Vitamin D.

It thus suppresses the Th1 pathway & induces the Th2 pathway by inhibiting the cytokines such as interferon-gamma (IFN), tumor necrosis factor – alpha & IL-12 and increasing Th2 cells and corresponding cytokines IL-4, IL-5, IL-10 & IL-13. This reaction is beneficial in combating the symptoms of some chronic conditions & autoimmune disorders like RA^[18].

Vitamin D and Rheumatoid Arthritis: Some Reviews

The Iowa Women's Health Study, a prospective cohort study conducted in 2004 by Merlino et al., 29,368 women aged 55–69 years, they found that greater intake of vitamin D might be associated with a lower risk of RA. Through 11 years of follow up, 152 cases of RA were reported. Greater intake of vitamin D was found to be inversely associated with risk of RA^[19,20].

Patel *et al.* in the year 2007 found an inverse relationship between 25(OH)D levels and DAS28. Rheumatoid Arthritis disease activity can be measured by various versions of the DAS SCALE one of them being the DAS-28 SCORE which takes into context tender and swollen joint count 1-28, patient assessed Global health score (0-100) and Hb% and ESR values^[21].

Hong Q et al., in 2013 conducted a study to compare Vitamin D status with levels of cytokines, disease severity & degree of bone loss in patients with RA. 130 patients were recruited from a hospital in China who were matched by 80 age & sex matched healthy controls. Statistical analysis revealed that RA patients had significantly lower Vitamin D compared to controls. Vitamin D levels were negatively associated with DAS 28. In RA, individuals with osteoporosis and osteopenia had significantly lower levels of Vitamin D. Finally, Vitamin D levels were negatively associated with IL-17 & IL-23 levels^[22].

Rheumatoid Arthritis & Atherosclerosis: Lipid Paradox

The most common cause of death in patients with RA is cardiovascular disease. The incidence of coronary artery disease and carotid atherosclerosis

is higher in RA patients than in the general population even when controlling for traditional cardiac risk factors, such as hypertension, obesity, hypercholesterolemia, diabetes, and cigarette smoking. Furthermore, congestive heart failure (including both systolic and diastolic dysfunction) occurs at an approximately twofold higher rate in RA than in the general population. The presence of elevated serum inflammatory markers appears to confer an increased risk of cardiovascular disease in this population^[23].

Cardiovascular Risk in Rheumatoid Arthritis: Recent Advances

Inflammation is linked with accelerated atherosclerosis & paradoxical inversion of the relationship between CV risk & lipid levels in patients with untreated RA. Inflammation is associated with qualitative & quantitative changes in lipoproteins with the anti-inflammatory & atheroprotective roles associated with HDL cholesterol significantly altered. In light of this, EULAR recommendations for management of CV risk in RA recommend disease control & annual CV risk assessment^[23].

HDL- A Potential Victim in RA: Although HDL's value as a marker in CV is unclear for most populations, they write, in patients with RA its anti-atherogenic properties may make it a valuable marker for CV risk. Systemic inflammation with RA induces both quantitative & qualitative changes to the HDL molecule by reducing its anti-inflammatory & anti-atherogenic properties and altered HDL sub-particle composition. It reduces Apolipoprotein-A-I in patients with active RA. Levels of paraoxonase-1, an anti-oxidant enzyme associated with HDL, are lower in patients with RA compared with healthy controls. Furthermore, DMARDs might also have some effects on the lipid profile. Methotrexate is the most widely used anchor drug in RA & its anti-inflammatory properties are not fully understood^[24]. It increases the total cholesterol, LDL, HDL & triglyceride levels in RA. These effects are believed to be due the inflammatory-damping

effects of Methotrexate. Also, anti- TNF alpha agents have been found to alter the lipoprotein spectrum by increasing LDL, total cholesterol & decreasing HDL^[25].

Few literatures in the pivotal role of HDL in RA outcome & mortality are as follows:

Lazarevic et. al., in 1992 first showed the paradoxical lipid profile in RA. George Steiner et al in a study conducted in the year 1997 also showed that RA is associated with an abnormal lipoprotein pattern i.e. principally low level of high-density lipoprotein (HDL) cholesterol. Most treatments for RA tend to improve the atherogenic index (total/HDL cholesterol ratio), with more evidence for biologics in this regard. The improvement in the lipoprotein profile in RA appears to be associated with suppression of inflammation^[26].

In a study by Park *et al.*, in the year 1999, the relationship between inflammatory state in RA and the disturbed HDL and apoprotein metabolism was explained. Forty-two patients with RA and 42 age and sex matched controls were studied. Patients with RA had not been treated with corticosteroid or disease modifying antirheumatic drugs prior to the study. Total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, apolipoprotein A1 (apo A1), apolipoprotein B (apo B), lipoprotein(a) [Lp(a)], and C-reactive protein (CRP) were measured in both groups and it was seen the levels of apo A1 and HDL-cholesterol were significantly lower in patients than in controls (128.5 vs. 151.8 mg/dl, 41.2 vs. 54.9 mg/dl, respectively)^[27].

Several studies done by Pincus *et al.* in the year 2001 concluded that RA patients had risk of heart attacks, stroke, and premature death due accelerated atherosclerosis in RA. They further found that this could be controlled on by lifestyle modification^[28].

Conclusion

Vitamin D deficiency is very common in India about 50-90% in all age groups and in both sexes and throughout the globe. This low Vitamin D

level has been implicated as an independent risk factor in RA development and progression. Hence, its serum levels can be estimated to measure disease activity in RA using DAS 28 and adequately supplemented in addition to conventional therapy. The other significant association of RA is with dyslipidemia which also contributes to its morbidity & mortality RA is associated with an abnormal lipoprotein pattern, principally low levels of high density lipoprotein (HDL) cholesterol, elevated total cholesterol (TC) and low density lipoprotein (LDL).The anti-inflammatory function of HDL and its correlation with systemic inflammation in RA patients has received only moderate attention and hence we should try to establish the correlation of HDL –C with disease activity in RA if any using the DAS-28 scale.

Conflict of Interest: Nil

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