

Correlation of Vitamin-D with Disease Severity and Psychological Effect in Rheumatoid Arthritis Patients

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Abstract

Vitamin D is either directly absorbed from food or produced in the skin behind exposure to UVB rays. In the kidneys and liver, Vitamin D is hydroxylated to create 1,25(OH)₂D, which has been demonstrated to have potent immunomodulatory characteristics. Rheumatoid arthritis (RA) and other autoimmune illnesses have been linked to Vitamin D deficiency, and it is thought to have anti-inflammatory and immunomodulatory characteristics. Significant treatment implications arise from the hypothesis that the severity of RA is associated with serum Vitamin D levels. The anti-inflammatory effects of Vitamin D are expected to be refereed at sites of RA disease, notably the inflamed joint. The active form of vitamin D, 1,25-dihydroxy vitamin D₃ (1,25(OH)₂D₃), may be implicated in these actions. This study compares a study with 100 volunteers, 50 RA sufferers and 50 healthy controls, all of whom were between the ages of 18 and 75. Vitamin D serum levels have been measured and compared between patients and controls. Levels of Vitamin D in RA patients were also examined at various steps of disease activity to ascertain whether there is an association between the two where 84% of RA patients reported Vitamin D deficiency compared to 34% of controls. In "RA patients serum Vitamin D levels" are also significantly lower than in the controls. There was a strong inverse connection between Vitamin D levels in serum and RA disease activity.

Patients with osteoarthritis (OA) experience negative effects on their mental health. In addition to their physical symptoms, people with rheumatoid arthritis (RA) may also suffer psychological difficulties such as worry and sadness. It is clear that the central nervous system can be impacted through both psychological stress & persistent inflammatory illnesses. Long-term exposure to high amounts of cytokines such as "tumour necrosis factor (TNF)", IL-6, and IL-1 in RA may result in inappropriate behaviours such as anhedonia, anorexia, fatigue, and depression as a result of disease.

Keywords: Psychological effect , Rheumatoid arthritis patients, autoimmune illnesses disease activity.

1. Introduction

Vitamin D stimulates calcium absorption in the stomach and holds adequate serum phosphate & calcium concentrations, which are necessary for regular bone mineralization and the prevention of hypocalcemic tetany. It is also utilized by osteoblasts and osteoclasts for bone growth and repair. Additionally, Vitamin D has a

number of roles in the body, including controlling immune, neuromuscular, and anti-inflammatory responses, as well as cell formation. Several genes that code for proteins that control differentiation, cell division, and death are regulated by vitamin D.

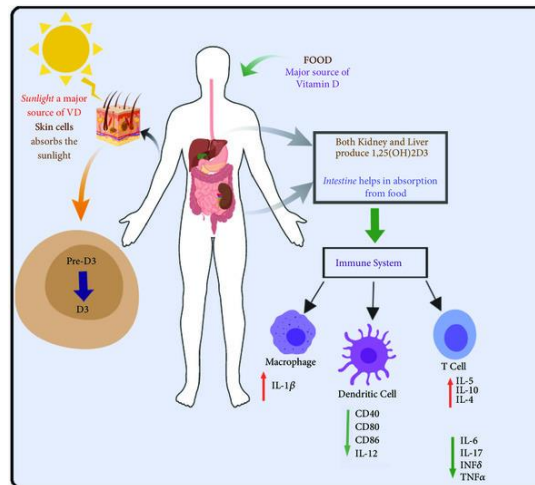


Figure 1: Route map of Vitamin D from production to action

(Source: <https://static.hindawi.com/articles/bmri/volume-2019/3494937/figures/3494937.fig.001.jpg>)

The identification of Vitamin D receptors (VDRs) in peripheral lymphocytic blood cells provides proof that Vitamin D controls immunological function. The “production of interferon-gamma, tumor necrosis factor-alpha”, and the T helper cell cytokine IL-2 is decreased in Vitamin D deficiency, and the development of T cells, antigen-presenting cells, and T cells is inhibited. The hypothesis that vitamin D's immunomodulatory properties are especially beneficial in this population supports the vitamin's therapeutic usage in Rheumatoid Arthritis (RA) patients.

2. Review of the literature

According to Heidari *et al.* 2019, Vitamin D deficiency is quite prevalent, particularly in people with autoimmune & musculoskeletal disorders. Vitamin D deficiency affects people differently depending on their diet, ethnicity, geography, season, and level of air pollution, among other factors.

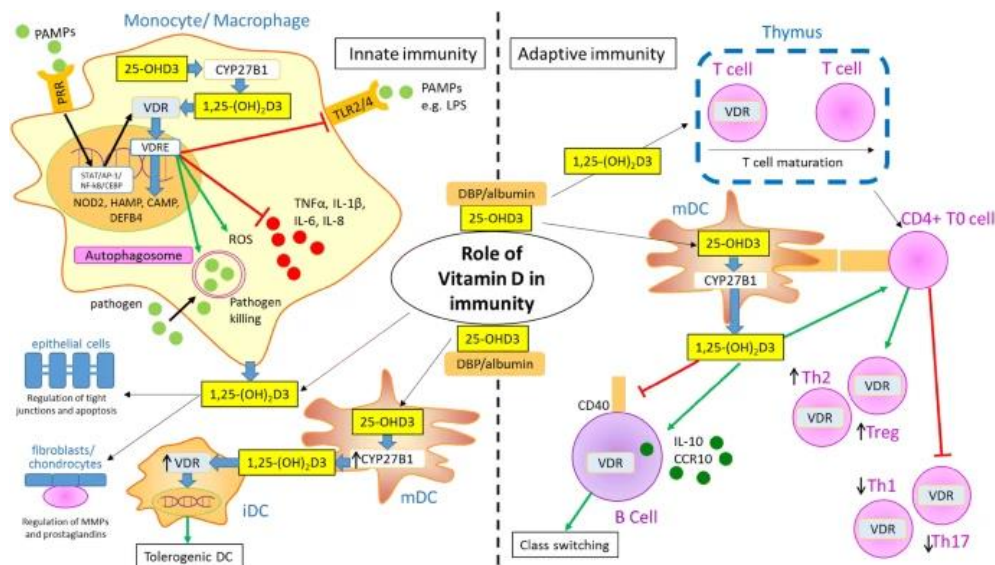


Figure 2: Role of Vitamin D in Rheumatoid Arthritis

(Source: https://media.springernature.com/lw685/springer-static/image/art%3A10.1007%2Fs00223-019-00577-2/MediaObjects/223_2019_577_Fig1_HTML.png?as=webp)

Vitamin D deficiency and immunopathogenesis and activity of RA

“Immune cells express Vitamin D receptors” (VDR), and synthesize the biologically significant metabolite of vitamin D3 which is 1,25(OH)₂D. Immune cells, especially dendritic cells, and macrophages of the paracrine and autocrine system, convert 25(OH)D to 1,25(OH)₂D.

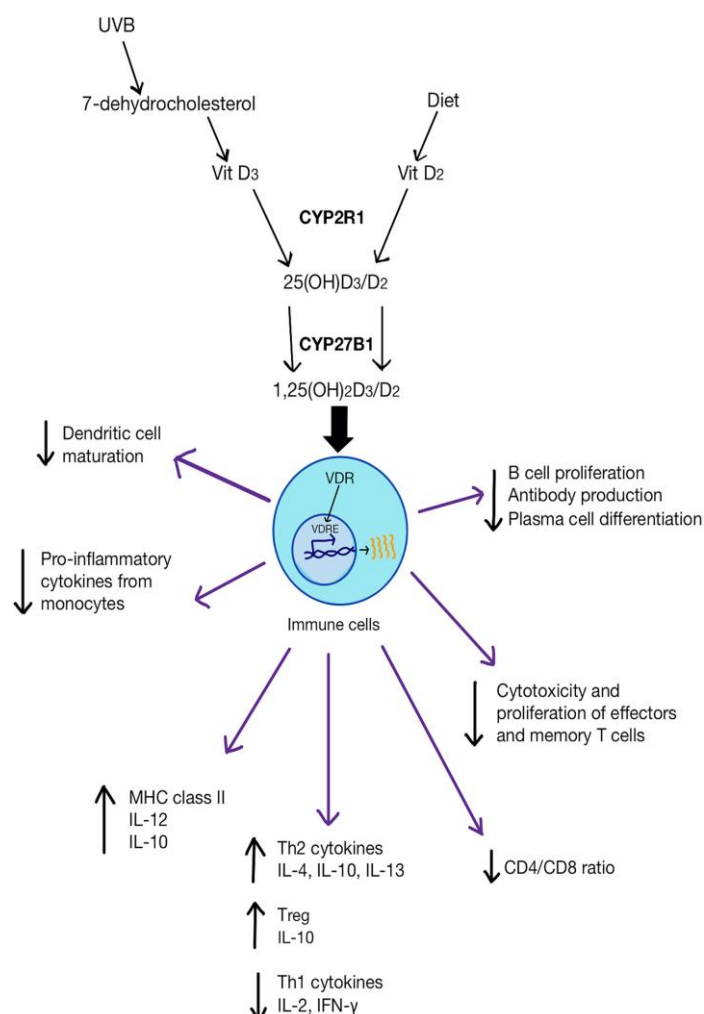


Figure 3: Vitamin D(both D3 and D2) metabolic pathway

(Source: https://www.frontiersin.org/files/Articles/616483/fimmu-11-616483-HTML/image_m/fimmu-11-616483-g001.jpg)

The emergence of lower serum 25(OH)D in RA may be due to inflammation since Vitamin D is an “acute-phase protein” and may reduce during an acute inflammatory response. Low Vitamin D stages in RA patients may therefore be a sign of inflammation rather than the cause of the disease's symptoms (Heidari *et al.* 2019). Therefore, the inflammatory method may confound the relationship between serum 25(OH)D and infection activity in RA.

Vitamin intake and RA

It has been found that there is an antagonistic relationship between Vitamin D & Rheumatoid Arthritis (RA) (Li *et al.* 2019). Increased Vitamin D intake was linked with a 34% lower risk of RA. There is no link between dietary Vitamin D intake and the effect of RA or “systemic lupus erythematosus”, according to numerous prospective longitudinal studies.

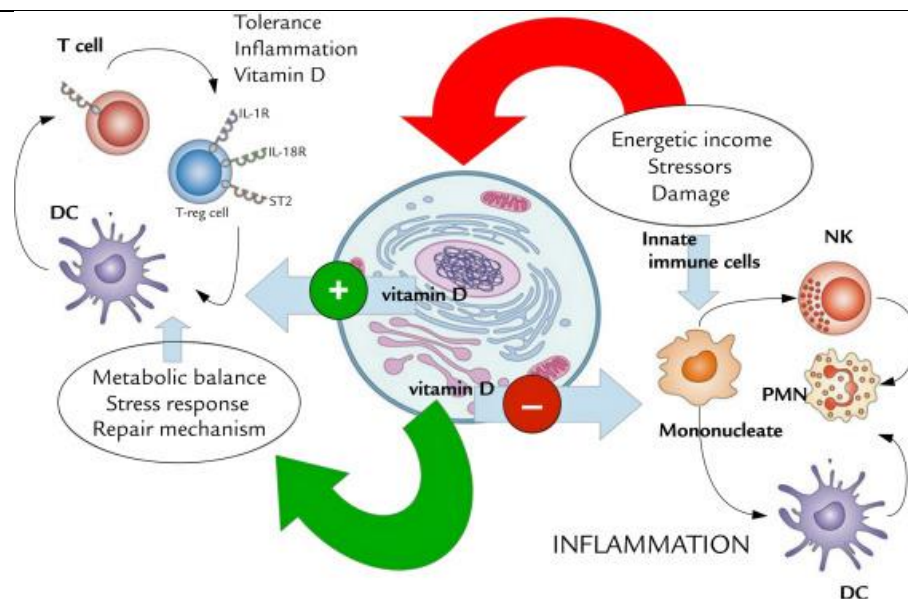


Figure 4: Role of Vitamin Din the immune system

(Source: <https://ars.els-cdn.com/content/image/1-s2.0-S0149291817302357-gr1.jpg>)

According to one study, there is no connection between the presence of “anti-cyclic citrullinated peptide antibodies”, serology for rheumatoid factor, or blood Vitamin D deficiency several years before RA is diagnosed. A separate study found that those who did not get enough Vitamin D did not have an increased risk of developing RA (Sirbu *et al.* 2020). Sunlight exposure is the main source of Vitamin D for humans, and as dietary intake only accounts for a small percentage of the body's needs, it is not usually correlated with blood levels of 25(OH)D. This makes it challenging to establish a link between Vitamin D consumption and the development of RA. Furthermore, because RA is a complex illness, both inherited and environmental factors can affect how it progresses.

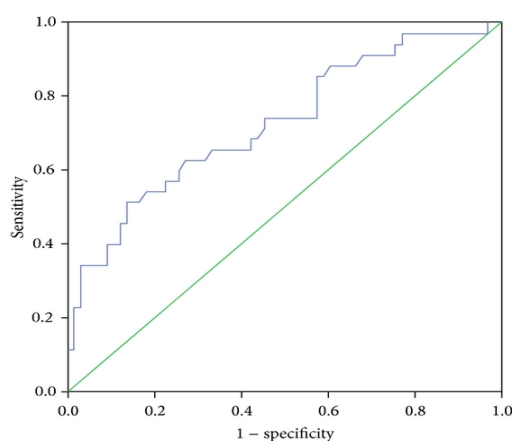


Figure 5: Vitamin D Is a Good Marker for Disease Activity of Rheumatoid Arthritis Disease

(Source: <https://static.hindawi.com/articles/dm/volume-2015/260725/figures/260725.fig.003.jpg>)

From the different literature, it is proven that Vitamin D is a good marker of Disease activity (Khajoei *et al.* 2019). The above curve is the ROC curve used for determining the optimal vitamin D cutoff point in expecting high disease activity.

3. Materials and Methodology

Materials

The connection between Vitamin D levels and disease severity in “rheumatoid arthritis patients” can be examined using 100 volunteers separated into two groups. The volunteers can be ranged in age between 18 to

75. There can be 50 RA cases in the first group and on the other hand 50 healthy individuals can be used as controls in the second group.

Inclusion criteria

According to the “American College of Rheumatology-European League” Against Rheumatism both females and males suffering from RA and who fall in the age group of 18–75 years 2010 can be enrolled in this study.

Exclusion criteria

Patients with nutritional deficiencies, issues with the liver or kidneys, hyperthyroidism, hyperparathyroidism, diabetes mellitus, or who have recently used Vitamin D supplements may not be included in this study. Diuretic, anticonvulsant, and thyroxine-taking patients can also be excluded from this study.

Methodology

All participants may be asked about their personal information, and a thorough history about the age at which symptoms first appeared, the progression of the illness and the distribution of its manifestations in the joints, the presence of any pain or swelling in the joints, and medication use may be obtained from cases. The disease activity score of 28 joints (DAS28) of people with RA can be calculated in accordance with the American College of Rheumatology criteria, and the results are shown as low, moderate-, and “high-disease activity”. The score of DAS28 can be calculated by doing the following activities -

- Calculating the number of joints that are inflamed joints out of 28
- Estimating the number of joints that are tendered out of 28
- The measuring of erythrocyte sedimentation rate (ESR) by taking blood
- Questioning the volunteers to create a global assessment of health that can be marked by indicating the 10-point line between very bad and very good levels.

4. Results and Discussion

Determination of mean serum calcium and Vitamin D levels

Group	Number	Mean serum calcium (mg/dl)	Mean serum vitamin D (ng/ml)	P
Rheumatoid arthritis	50	8.54±0.62	21.05±10.02	<0.05
Controls	50	9.01±0.59	32.87±14.16	

Table 1: Mean serum calcium and Vitamin D levels in the study groups

(Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5812075/bin/JNSBM-9-54-g001.jpg>)

The above table represents the mean level of serum calcium and Vitamin D among the volunteers of the study group. In the study group, the mean age of participants who are suffering from RA is 44.92 ± 13.06 years and the mean age of healthy participants who are considered as the control is 44.02 ± 11.65 years. In the test group, 14 percent of participants that is 7 are male and 43 percent of participants that is 43 are female out of 50 participants (Sinha *et al.* 2022). On the other hand, in the control group, 8 participants which means 16 percent of the total 50 participants are male, and 42 which means 84 percent of participants out of the total are female. After doing the tests, the results are represented in the above table where the mean calcium level in serum is 8.54 ± 0.62 mg/dl in the test group that is in the RA group. On the other hand, in the control group, the mean serum calcium level is 9.01 ± 0.59 mg/dl. In this case, the difference is significant that is the p-value is less than 0.05. In the RA group, a total of 42 patients about 84 percent of patients had a mean Vitamin D level below 30 ng/ml which indicates Vitamin D deficiency whereas only 34 percent people that is 17 participants are from the control group having Vitamin D deficiency. In the control group, the mean Vitamin D in serum is 32.87 ± 14.16 ng/ml, and in the RA group, the mean Vitamin D in serum is 21.05 ± 10.02 ng/ml. In this case, this difference is also statistically significant which is below the P value.

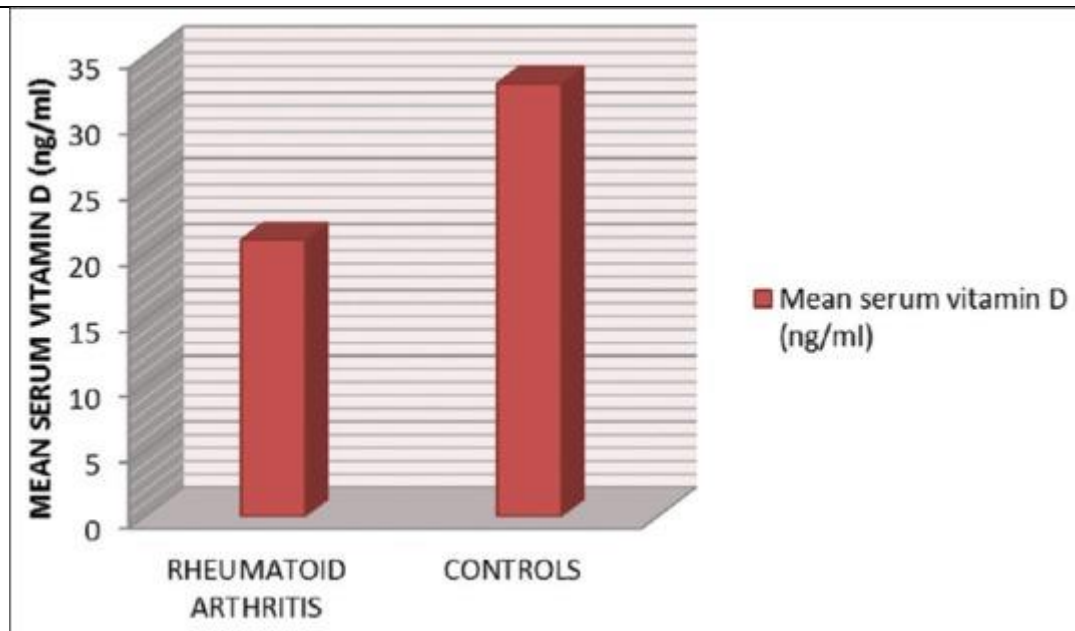


Figure 3: Graphical representations of mean serum Vitamin D levels in rheumatoid arthritis patients and controls
(Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5812075/bin/JNSBM-9-54-g002.jpg>)

The above graph is the representation of the mean Vitamin D level in serum in both the group such as the control and the Rheumatoid arthritis group. The x-axis of the graph is represented as the participant group and the y-axis represents the mean serum Vitamin D in ng/ml.

Determination of mean serum calcium and Vitamin D levels in rheumatoid arthritis patients according to their disease activity

Group (according to disease activity)	Number	Mean serum calcium (mg/dl)	Mean serum vitamin D (ng/ml)	P
Remission	6	8.96±0.75	35.28±9.0	<0.05
Low	3	8.83±0.05	33.80±4.1	
Moderate	19	8.76±0.60	22.47±6.18	
High	22	8.19±0.47	14.21±6.97	

Table 2: Mean serum calcium and Vitamin D levels in rheumatoid arthritis patients according to their disease activity

(Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5812075/bin/JNSBM-9-54-g003.jpg>)

The above table is the statistical outcomes of the mean “serum calcium and Vitamin D levels” in “rheumatoid arthritis patients” according to their disease activity. Out of 50 patients suffering from RA, 12 percent of patients have a DAS28 score below 2.6 whereas 6 percent are belongs to the low disease activity group, and around 19 percentage patients are in the moderate activity group with a DAS28 score is in between 2.7 - 3.3, and finally, 44 percent patients are in the group of high disease activity group where the DAS28 score is above 5.1 (Shevchenko and Khadzhynova, 2019). And the difference between the different levels of disease activity is within the statistically significant range that is the value of P value is less than 0.05.

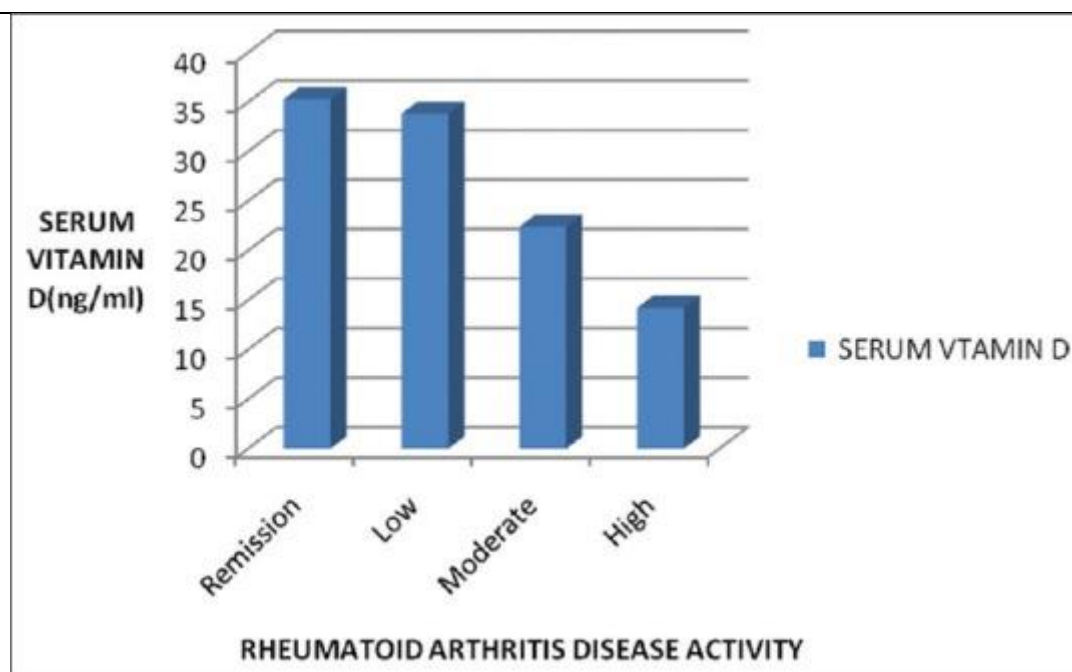


Figure 4: Graphical representations of mean serum Vitamin D levels in rheumatoid arthritis patients according to their disease activity

(Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5812075/bin/JNSBM-9-54-g002.jpg>)

The above bar graph represents the mean serum Vitamin D levels in “Rheumatoid arthritis patients” according to their infection activity. The x-axis of the graph represents the Rheumatoid arthritis disease activity, and the y-axis represents the serum Vitamin D level in ng/ml. From the graph, it is very clear that the serum Vitamin D level is inversely proportional to the Rheumatoid arthritis disease activity. The disease activity is maximum when the serum Vitamin D level is low and vice-versa.

5. Conclusion and future scope

In people with RA, Vitamin D insufficiency is more common and may contribute to the onset or progression of the illness. The serum levels of Vitamin D in RA tend to drop as the disease activity rises. To be sure that they are taking the proper dosage, all RA patients should have their Vitamin D levels thoroughly evaluated. Before vitamin D's immunomodulatory, anti-inflammatory, and antiproliferative capabilities can be employed to treat a range of autoimmune rheumatic diseases, more research must be done in this area.

Recommendations

Low serum levels of 25(OH)D3 are now known to be a feature of inflammatory disorders like RA, despite some data suggesting that Vitamin D levels in RA patients are not necessarily lower than those of healthy controls. The body's ability to absorb calcium, which is essential for healthy bone formation, is aided by vitamin D. It has been shown that increasing Vitamin D consumption can lessen the symptoms of rheumatoid arthritis. Thus, it can be recommended that people must be exposed to sunlight to intake Vitamin D which not only enhance the anti-inflammatory response but also helps in the absorption of calcium in blood serum.

Psychological Impact on the patients

Chronic illness of rheumatoid arthritis (RA) has a negative impact on the physical, emotional, and psychological health of persons who have it. According to earlier studies, persons who have the illness feel more anxious and despairing than the ordinary person. Another condition that may be important is ego resilience, the capacity to adjust one's level of self-control to suit the requirements of the current scenario. Because it has been given the responsibility of controlling the choice of coping strategy, ego resilience is viewed as one of the most significant helpful techniques for dealing with stressful situations.

People who have higher levels of ego resilience employ crisis-coping strategies that are more successful when they are ill, as a result, they are better able to balance both positive and negative emotions and display a higher

level of overall self-control. Furthermore, it has been discovered that ego saliency is associated with a propensity to select active coping strategies that increase efficacy and a sense of agency. One percent of the population globally suffers with rheumatoid arthritis (RA), a “chronic autoimmune inflammatory disease”. It might also show extra-articular symptoms that affect the body's other crucial organs. Cognitive impairment, depression, and anxiety are more prevalent in RA patients than in the overall healthy population.

Due to fatigue and physical suffering, these mental health issues cause RA patients to be less receptive to treatment and more active in the condition. A percentage of anxiety and depression can be reduced by RA medications, but not entirely. Depression makes it difficult for RA patients to manage their physical symptoms, such as fatigue and discomfort. Major psychiatric disorders including depression and anxiety can be connected to RA through biological and cytokine-related pathways as well as the psychological effects of prolonged physical suffering on patients' mental health. Patients with RA who have "patient-reported outcomes (PROs)" including morning stiffness, tiredness, and constant physical discomfort report these symptoms most frequently. Additionally, these PROs increase disease activity and are likely to make depression worse. It is evident that both psychological stress and chronic inflammatory diseases can impact the central nervous system. Long-term exposure to high levels of “cytokines including tumor necrosis factor” (TNF), IL-6, and IL-1 in RA may cause maladaptive behaviours in the face of illness, including anhedonia, anorexia, tiredness, and depression. Depression is characterized by low mood, low self-esteem, tiredness, insomnia, lethargy, psycho-motor dysfunction, and continuously pessimistic thinking (Link.springer.com, 2020).

Reference

- [1] Li, D., Jeffery, L.E., Jenkinson, C., Harrison, S.R., Chun, R.F., Adams, J.S., Raza, K. and Hewison, M., 2019. Serum and synovial fluid vitamin D metabolites and rheumatoid arthritis. *The Journal of steroid biochemistry and molecular biology*, 187, pp.1-8.
- [2] Sirbu, E., Buleu, F., Tudor, A. and Dragan, S., 2020. Vitamin D and disease activity in rheumatoid arthritis patients: a retrospective study in a Romanian cohort. *Acta Biochimica Polonica*, 67(2), pp.267-272.
- [3] Khajoei, S., Hassaninevisi, M., Kianmehr, N., Seif, F., Khoshmirsafa, M., Shekarabi, M., Samei, A. and Haghighi, A., 2019. Serum levels of adiponectin and vitamin D correlate with activity of Rheumatoid Arthritis. *Molecular biology reports*, 46, pp.2505-2512.
- [4] Sinha, P., Kumari, R., Runu, R., Kumar, S., Ranjan, R.K., Shekhar, R., Keshari, J.R. and Kumari, S., 2022. Assessment of Vitamin D3 level in patients of rheumatoid arthritis and its relationship with disease activity using DAS 28-CRP in tertiary care center of Bihar, India. *Asian Journal of Medical Sciences*, 13(12), pp.85-91.
- [5] Shevchenko, N. and Khadzhynova, Y., 2019. Juvenile idiopathic arthritis and vitamin D status in Ukrainian patients. *Georgian Med News*, 294, pp.88-91.
- [6] Heidari, B., Hajian-Tilaki, K. and Babaei, M., 2019. Vitamin D deficiency and rheumatoid arthritis: epidemiological, immunological, clinical and therapeutic aspects. *Mediterranean journal of rheumatology*, 30(2), pp.94-102.
- [7] Kemeriz, F., Tuncer, S.Ç., Acar, E.M. and Tuğrul, B., 2020. Evaluation of 25-hydroxy vitamin D levels and disease severity in patients with acne vulgaris. *Dermatologic Therapy*, 33(3), p.e13393.
- [8] Kaur, N. and Sarao, P.K., 2023. Assessment of disease activity score with respect to vitamin D in rheumatoid arthritis. *International Journal of Orthopaedics*, 9(2), pp.142-144.

Website

- [9] Link.springer.com, 2020, *Rheumatoid Arthritis: The Impact of Mental Health on Disease: A Narrative Review*, Available at: <https://link.springer.com/article/10.1007/s40744-020-00217-4> [Accessed on: 08.06.2023]