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Original Research Article

The Relationship between Vitamin D Deficiency and Immune Dysregulation in Rheumatoid Arthritis (RA) Patients

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Abstract: ***Background*:** Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation, joint destruction, and immune dysregulation. Vitamin D, a key regulator of the immune system, has been implicated in various autoimmune diseases, including RA. However, the exact role of vitamin D in immune modulation and its potential relationship with immune markers in RA patients remains underexplored. ***Objective*:** This study aimed to investigate the relationship between vitamin D deficiency and immune dysregulation in RA patients, with a focus on inflammatory markers, cytokines, and regulatory T-cells. ***Methodology*:** A cross-sectional study was conducted from 1st January to 30th August 2024, including 100 RA patients (50 males, 50 females) and 50 control participants (25 males, 25 females). Blood samples were collected from all participants to measure serum vitamin D levels, inflammatory markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]), and immune parameters (IL-10, IL-17, and regulatory T-cells). Data were analyzed using correlation analysis to examine relationships between vitamin D levels and immune parameters. ***Results*:** RA sufferers exhibited drastically decrease nutrition D degrees as compared to controls (18.5 ± 6.2 ng/mL vs. 32.1 ± 7.8 ng/mL, $p < 0.001$). Additionally, better inflammatory markers had been determined in RA patients, with CRP and ESR levels considerably expanded compared to controls ($p < 0.001$). A widespread high-quality correlation turned into found among vitamin D stages and IL-10 ($r = 0.582$, $p < 0.001$) and regulatory T-cells ($r = 0.421$, $p < 0.001$), whilst an inverse correlation changed into determined with IL-17 ($r = -0.645$, $p < 0.001$). Moreover, a terrible correlation between vitamin D stages and ESR ($r = -0.512$, $p < 0.001$) become additionally cited, suggesting a link between nutrition D deficiency and systemic irritation in RA. ***Conclusion*:** The outcomes of this observe assist the position of diet D in immune modulation and irritation in RA patients. Vitamin D deficiency turned into associated with better inflammatory markers and adjusted immune responses, together with accelerated levels of seasoned-inflammatory cytokines (IL-17) and reduced regulatory T-cellular characteristic. These findings highlight the potential therapeutic function of vitamin D supplementation in managing immune dysregulation and infection in RA. Further studies are had to affirm these outcomes and discover the medical benefits of diet D in RA remedy.

Keywords: Rheumatoid Arthritis (RA), Vitamin D Deficiency, Immune Dysregulation, Pro-Inflammatory Cytokines and Regulatory T-cells.

INTRODUCTION

Rheumatoid arthritis (RA) is a continual, inflammatory autoimmune ailment that in general impacts the joints. The condition occurs whilst the immune system, that's commonly accountable for defending the frame towards dangerous invaders like microorganism and viruses, mistakenly attacks the frame's very own healthful tissues. This effects in irritation in the synovial membrane that lines the joints, leading to pain, swelling, stiffness, and eventually joint damage. The inflammation can also affect other organs, along with the pores and skin, lungs, and eyes, making RA a systemic situation. Over time, if untreated, the chronic irritation can cause irreversible harm to the joints and a decline in universal feature (Charoenngam, 2021).

RA is considered an autoimmune disorder due to the fact the immune machine turns into hyperactive and assaults healthful tissue. While the exact motive of RA stays uncertain, several elements make a contribution to the improvement of the disorder. Genetics play a vast position, with sure genes growing the threat of developing RA. Environmental factors, which includes smoking, infections, and strain, are also thought to cause or exacerbate the sickness in the ones genetically predisposed. These factors disrupt the everyday immune response, causing an atypical activation of T-cells and different immune machine additives, which ends up in the production of seasoned-inflammatory cytokines and antibodies that assault the body's very own tissues. The joint damage because of RA is due to this sustained inflammatory response, which damages cartilage, bone, and ligaments (Bishop *et al*., 2021).

The immune device itself is a complex network of cells, tissues, and organs designed to protect the frame from infection and disease. It can be divided into primary components: the innate immune device, which presents the primary line of protection and responds fast to a wide range of pathogens, and the adaptive immune machine, which affords an extra unique and focused response. The immune system is predicated on quite a number cells, including T-cells, B-cells, macrophages, and dendritic cells, to pick out and damage pathogens. However, in autoimmune sicknesses like RA, this complicated network fails to differentiate among overseas invaders and the frame's very own cells, main to the development of chronic inflammation and tissue damage (Fletcher, *et al*., 2022).

Vitamin D is a fat-soluble nutrition that performs a critical position in preserving average health. Known normally for its function in regulating calcium and phosphate levels within the frame, which can be critical for bone health, vitamin D also has a profound effect on the immune machine. It is produced within the skin in response to sunlight, however also can be obtained from nutritional resources like fish, eggs, and fortified ingredients. Vitamin D facilitates modulate the immune system by influencing the hobby of immune cells, together with T-cells, B-cells, and dendritic cells, which might be critical for immune responses. It does this by using binding to vitamin D receptors on those immune cells, leading to the law of inflammatory responses (Ruiz-Ballesteros, *et al*., 2021).

In unique, vitamin D has been proven to have an inhibitory impact on the manufacturing of seasoned-inflammatory cytokines, which can be involved within the improvement of autoimmune illnesses like RA. By regulating the immune system and promoting anti-inflammatory responses, nutrition D facilitates prevent the immune system from attacking the frame's personal tissues. Some studies endorse that insufficient tiers of vitamin D may contribute to the onset of RA or worsen the disease in individuals who have already got it. Deficiency in diet D has been connected to an improved hazard of growing autoimmune conditions and is associated with better sickness activity in sufferers with RA. This has led researchers to analyze whether or not supplementing diet D should reduce the severity of RA signs and symptoms or maybe prevent its onset in at-hazard people (Ishikawa, *et al*., 2017).

Vitamin D deficiency is not unusual international, and its occurrence is especially excessive among human beings with autoimmune diseases. Factors which includes restricted solar publicity, terrible dietary consumption, and the frame's inability to effectively soak up diet D make contributions to low levels of this crucial nutrient. In RA patients, studies have shown that low levels of diet D are correlated with higher disorder interest, multiplied inflammation, and extra intense joint harm. As a result, there's developing hobby in the capability therapeutic consequences of vitamin D supplementation in RA sufferers. Evidence shows that restoring ok nutrition D degrees can assist lessen irritation, improve ailment hobby, and enhance the efficacy of conventional RA remedies. Nonetheless, the precise mechanisms via which diet D impacts the immune gadget and RA progression are still not fully understood, and in addition studies is needed to decide the most useful tiers of vitamin D required for RA management (Nikolaus, *et al*., 2013; Olsen, *et al*., 2016). This take a look at pursuits to evaluate the affiliation between serum nutrition D ranges and immune dysregulation in RA patients, focusing on inflammatory markers and cytokine profiles.

METHODOLOGY

A go-sectional have a look at become performed over a duration of 8 months, from 1st January to thirtieth August 2024, regarding 150 contributors. The have a look at populace covered a hundred rheumatoid arthritis (RA) sufferers (50 men and 50 females) and 50 control contributors without RA. Participants had been recruited from Tikrit Teaching Hospital and orthopedic outpatient clinics inside the governorate. The take a look at population protected one hundred rheumatoid arthritis (RA) sufferers (50 men and 50 females) and 50 control members with out RA, age between (35-75 years), and no large comorbidities that might have an effect on diet D tiers or immune characteristic. Patients with conditions like chronic kidney disease or other autoimmune problems were excluded from the look at.

Blood samples had been collected from every patient after knowledgeable consent became obtained. The serum vitamin D tiers were measured by using Enzyme-Linked Immunosorbent assay (ELISA). Inflammatory markers, which includes C-reactive protein (CRP) and erythrocyte sedimentation price (ESR), were additionally measured via using (Spectrophotometer). Immune parameters, along with cytokine stages (IL-10, IL-17) and regulatory T-mobile counts, had been assessed to observe immune dysregulation. They by the use of enzyme-linked immunosorbent assay (ELISA).

Demographic data, which include age and gender, have been collected. Clinical facts associated with RA, including disorder duration and severity, were also documented. Laboratory outcomes for nutrition D, inflammatory markers (CRP, ESR), and immune parameters (Regulatory T-cells) have been obtained from blood samples.

Statistical Analysis

Data analysis was conducted using SPSS software, version 22. Descriptive statistics were used to summarize demographic and clinical characteristics across groups. Comparative analyses (t-tests, ANOVA) were performed to assess differences between RA patients and controls. Correlation and regression analyses were applied to investigate relationships between vitamin D levels, inflammatory markers, and immune parameters. A significance level of $p < 0.05$ was used for all statistical tests.

RESULTS

The survey reveals significant gender differences in comorbid conditions (kidney or liver diseases) among RA patients. However, female RA patients showed a higher prevalence of genetic conditions and family history of RA, indicating potential hereditary and gender-specific influences (Table1).

Table 1: Survey Responses by Gender

Parameter	Male RA Patients (n=50)	Female RA Patients (n=50)	Male Controls (n=25)	Female Controls (n=25)
Kidney Disease (%)	12 (24%)	15 (30%)	3 (12%)	2 (8%)
Liver Disease (%)	8 (16%)	10 (20%)	2 (8%)	1 (4%)
Genetic Conditions (%)	10 (20%)	12 (24%)	3 (12%)	3 (12%)
Family History of RA (%)	15 (30%)	22 (44%)	0 (0%)	0 (0%)

The mean age of male RA patients was 54.8 ± 10.6 years, compared to 53.2 ± 9.3 years for male controls. Similarly, the mean age of female RA patients was 55.7 ± 10.3 years, compared to 54.5 ± 9.5 years for female controls. The differences in age across groups were not statistically significant ($p = 0.234$). Regarding RA disease duration, male patients reported a slightly longer mean disease duration (10.5 ± 4.8 years) compared to female patients (9.8 ± 5.4 years). This parameter was not applicable NA to controls, as they were not diagnosed with RA (Table 2, Figure1).

Table 2: Demographic and Clinical Characteristics of Study Participants

Characteristic	Male RA Patients (n=50)	Male Controls (n=25)	Female RA Patients (n=50)	Female Controls (n=25)	p-value
Age (mean ± SD, years)	54.8 ± 10.6	53.2 ± 9.3	55.7 ± 10.3	54.5 ± 9.5	0.234
Disease duration (years)	10.5 ± 4.8	NA	9.8 ± 5.4	NA	-

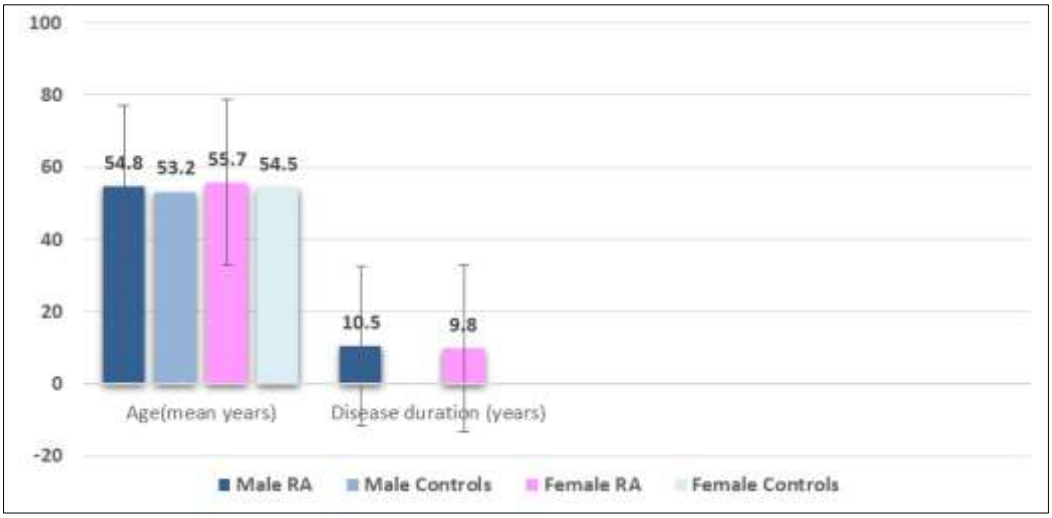

Figure 1: Demographic and Clinical Characteristics of Study Participants

Vitamin D levels were significantly lower in both male and female RA patients compared to their respective controls ($p < 0.001$). Male RA patients had 17.8 ± 5.9 ng/mL, and female RA patients had 19.2 ± 6.5 ng/mL. Male controls had 30.2 ± 7.6 ng/mL, and female controls had 34.1 ± 8.0 ng/mL. CRP (C-reactive protein) levels, a marker of inflammation, were higher in RA patients compared to controls ($p < 0.001$). Male RA patients had 13.2 ± 4.5 mg/L, while

male controls had 4.3 ± 2.3 mg/L. Female RA patients had 11.6 ± 4.0 mg/L, while female controls had 4.1 ± 2.0 mg/L. ESR (erythrocyte sedimentation rate), another marker of inflammation, was also significantly higher in RA patients compared to controls ($p < 0.001$). Male RA patients had 44.1 ± 11.0 mm/hour, while male controls had 19.6 ± 9.4 mm/hour. Female RA patients had 41.3 ± 10.6 mm/hour, while female controls had 21.0 ± 7.8 mm/hour.

IL-10 (Interleukin-10), an anti-inflammatory cytokine, was significantly elevated in both male and female RA patients compared to controls ($p < 0.001$). Male RA patients had 45.7 ± 14.2 pg/mL, while male controls had 15.3 ± 6.2 pg/mL. Female RA patients had 49.3 ± 15.1 pg/mL, while female controls had 16.8 ± 5.5 pg/mL. IL-17 (Interleukin-17), a pro-inflammatory cytokine, was significantly higher in RA patients compared to controls ($p < 0.001$). Male RA patients had 19.5 ± 5.4 pg/mL, while male controls had 6.4 ± 2.3 pg/mL. Female RA patients had 22.1 ± 6.3 pg/mL, while female controls had 5.8 ± 2.2 pg/mL. Regulatory T-cells (Tregs), that are crucial for immune law, were appreciably decreased in RA patients in comparison to controls ($p < 0.001$). Male RA sufferers had 7.5 ± 3.2%, and girl RA sufferers had 6.8 ± 3.1%. Male controls had 14.2 ± 4.1%, and lady controls had 15.00 ± 3.9% (Table 3, Figure 2).

Table 3: Laboratory Results: Vitamin D, Inflammatory Markers, Cytokines, and Interleukins

Parameter	Male RA Patients (n=50)	Male Controls (n=25)	Female RA Patients (n=50)	Female Controls (n=25)	p-value
Vitamin D (ng/mL)	17.8 ± 5.9	30.2 ± 7.6	19.2 ± 6.5	34.1 ± 8.0	<0.001
CRP (mg/L)	13.2 ± 4.5	4.3 ± 2.3	11.6 ± 4.0	4.1 ± 2.0	<0.001
ESR (mm/hour)	44.1 ± 11.0	19.6 ± 9.4	41.3 ± 10.6	21.0 ± 7.8	<0.001
IL-10 (pg/mL)	45.7 ± 14.2	15.3 ± 6.2	49.3 ± 15.1	16.8 ± 5.5	<0.001
IL-17 (pg/mL)	19.5 ± 5.4	6.4 ± 2.3	22.1 ± 6.3	5.8 ± 2.2	<0.001
Regulatory T-cells (%)	7.5 ± 3.2	14.2 ± 4.1	6.8 ± 3.1	15.0 ± 3.9	<0.001

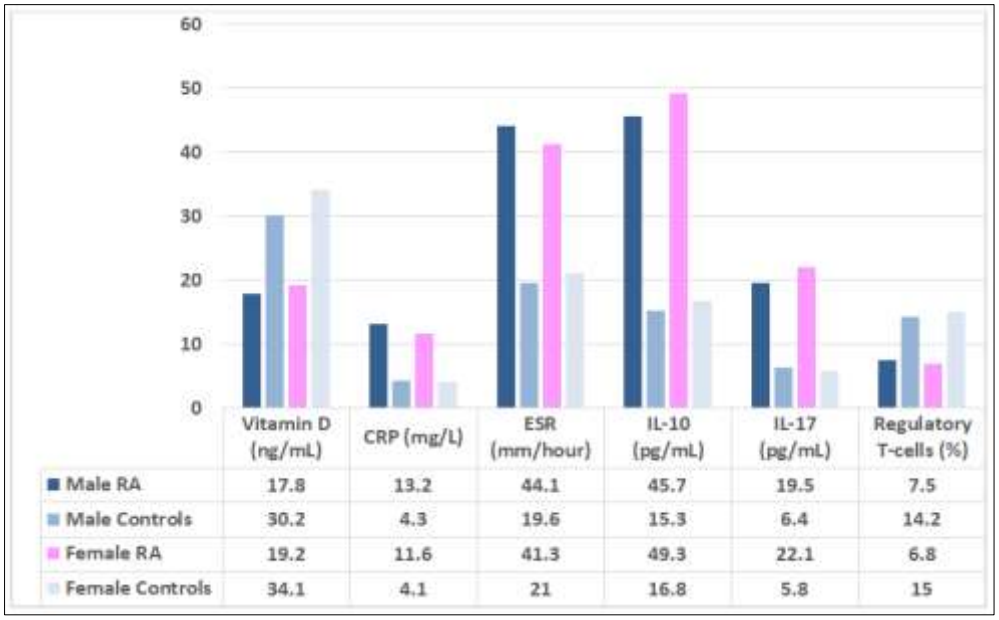

Figure 2: Laboratory Results

In precis, RA sufferers showed notably lower diet D levels and better inflammatory markers (CRP and ESR) compared to wholesome controls, in addition to improved IL-10 and IL-17 ranges, indicating immune dysregulation. Additionally, regulatory T-mobile possibilities had been notably lower in RA patients, similarly supporting the immune imbalance related to rheumatoid arthritis.

The statistics display that nutrition D has substantial correlations with diverse immune parameters in RA patients, helping its role in modulating immune responses and infection. Specifically, better vitamin D tiers appear to promote anti-inflammatory cytokines (IL-10) and regulatory T-cells, whilst being inversely associated with pro-inflammatory markers like IL-17 and ESR. These findings advise that preserving adequate diet D stages may help manage immune dysregulation and infection in RA patients.

The correlation among nutrition D levels and diverse immune parameters in RA sufferers is offered. There become a enormous positive correlation among nutrition D degrees and IL-10 ($r = 0.582$, $p < 0.001$). This suggests that better diet D stages are related to extended degrees of IL-10, an anti-inflammatory cytokine. It suggests that sufficient diet D may

beautify the anti-inflammatory response in RA patients. An inverse correlation changed into discovered among nutrition D degrees and IL-17 ($r = -0.645$, $p < 0.001$). This means that lower nutrition D ranges are associated with higher stages of IL-17, a pro-inflammatory cytokine. This inverse courting helps the idea that vitamin D deficiency may make a contribution to increased infection in RA.

A sizable fine correlation changed into also discovered between diet D stages and regulatory T-cells ($r = 0.421$, $p < 0.001$). This indicates that better vitamin D stages are related to an increase in regulatory T-cells, which might be important for immune law. This finding in addition supports the function of vitamin D in modulating immune responses. There changed into a massive inverse correlation among vitamin D levels and ESR ($r = -0.512$, $p < 0.001$). ESR is a marker of infection, and this negative correlation indicates that lower vitamin D stages are related to better ESR, reflecting extended systemic irritation in RA sufferers. This further emphasizes the capacity function of nutrition D in controlling inflammatory processe (Table 4).

Table 4: Correlation between Vitamin D Levels and Immune Parameters in RA Patients

Parameter	Correlation Coefficient (r)	p-value
Vitamin D vs. IL-10	0.582	<0.001
Vitamin D vs. IL-17	-0.645	<0.001
Vitamin D vs. T-cells	0.421	<0.001
Vitamin D vs. ESR	-0.512	<0.001

DISCUSSION

The relationship between vitamin D deficiency and rheumatoid arthritis (RA) has gained Extensive interest, with several studies investigating the potential position of diet D in both the onset and development of autoimmune sicknesses like RA. While the proof is blended, it's far clear that diet D plays a crucial function in immune regulation, and its deficiency may also contribute to the pathogenesis of RA.

Several studies have proven that diet D deficiency is common amongst people with autoimmune sicknesses, inclusive of RA (Salman Hosi *et al*., 2024). However, the precise mechanisms linking vitamin D reputation to RA continue to be doubtful. For instance, Gatenby *et al*., (2013) recommended that at the same time as nutrition D deficiency ought to affect the development of rheumatic diseases, further research is needed to verify its direct effect on RA onset. Similarly, Nielen *et al*., (2006) discovered no conclusive proof linking low vitamin D degrees to an accelerated threat of growing RA, highlighting the complexity of the disorder's pathogenesis, which likely includes genetic, environmental, and immune elements.

El-Gabalawy (2024) emphasized the broader effect of RA on prone populations, which includes First Nations groups, where the superiority of RA is growing. The have a look at harassed the want for centered strategies to prevent and manage RA in those populations, consisting of improving get entry to to healthcare and addressing vitamin D deficiency. This attitude underscores the importance of vitamin D as critical element in decreasing the risk and severity of RA, particularly in populations at higher risk because of socio-economic or environmental factors.

In comparison, research by way of Zakeri *et al*., (2016) and Harrison *et al*., (2020) have furnished evidence suggesting that low diet D degrees can be associated with higher ailment pastime in RA sufferers. Zakeri *et al*., (2016) determined that nutrition D deficiency turned into connected to better ailment interest in recent-onset RA patients, suggesting that vitamin D may not simplest impact disorder improvement however also modulate disorder severity. Similarly, Harrison *et al*., (2020) emphasized that maintaining top of the line vitamin D stages may additionally help reduce irritation and improve disorder outcomes in autoimmune situations like RA. These findings assist the ability healing blessings of vitamin D supplementation in lowering sickness activity and enhancing the best of lifestyles for RA sufferers.

Research by means of Alharbi *et al*., (2023) has further underscored the significance of vitamin D in RA sufferers, especially in Saudi populations. Their study determined that vitamin D deficiency is typical among RA sufferers in Saudi Arabia, with diet D ranges inversely related to ailment activity. This highlights the worldwide relevance of vitamin D deficiency in RA and similarly helps the perception that diet D supplementation may additionally function a beneficial adjunctive treatment for RA, particularly in areas wherein deficiency is common.

The position of genetic elements in diet D metabolism has also been a focal point of recent studies. Studies including those via Ruiz-Ballesteros *et al*., (2020) and Bagheri-Hosseinabadi *et al*., (2020) have highlighted how genetic variations in diet D receptor (VDR) genes may want to influence susceptibility to autoimmune sicknesses, which includes RA. These genetic variations, while blended with environmental factors like nutrition D deficiency, might also make

contributions to immune dysregulation in RA. These findings suggest that vitamin D's effects on the immune device may be prompted via an individual's genetic makeup, further complicating the connection between nutrition D and RA.

In terms of therapeutic implications, numerous research has explored the function of vitamin D supplementation in managing RA. Rondanelli *et al*., (2021) and Charoenngam (2021) reviewed the capacity blessings of keeping ok vitamin D levels for decreasing inflammation and enhancing RA symptoms. Both studies highlighted the importance of thinking about diet D as a part of a comprehensive approach to coping with RA. The findings of Zakeri *et al*., (2016) in addition help this, indicating that enhancing diet D popularity can also reduce disease activity and improve overall patient results.

Additionally, research analyzing the effect of vitamin D on immune cells and inflammatory markers have underscored the immunomodulatory role of diet D in RA. Vitamin D has been shown to steer the pastime of T cells, dendritic cells, and macrophages, all of which play a key function in the improvement of autoimmune diseases. Ao *et al*., (2021) discussed how diet D can lessen pro-inflammatory cytokines and enhance the function of regulatory T cells, which are vital for preserving immune balance in RA. These findings advocate that diet D might also assist modulate immune responses and alleviate irritation in RA sufferers. Despite these promising consequences, some studies, including Feser *et al*., (2009), have determined no great affiliation between vitamin D levels and RA-associated autoantibodies. This shows that at the same time as diet D can also affect sickness hobby, its effects on autoimmunity markers are greater complex and might depend upon different factors.

CONCLUSION

In end, nutrition D plays a key position in regulating the immune device, and its deficiency may additionally worsen immune dysregulation in RA. The relationship among diet D and RA ailment hobby is complex, encouraged by way of genetic, environmental, and immunological elements. While more studies is wanted to outline top of the line nutrition D levels and confirm supplementation blessings, present day proof highlights the significance of keeping adequate diet D ranges in dealing with RA and probably stopping disorder progression. Regular tracking of nutrition D popularity and thinking about supplementation can be beneficial in RA management.

Ethical Considerations

The study was permitted with the aid of the moral committee of Tikrit Teaching Hospital. Informed consent was acquired from all members, ensuring voluntary participation and understanding of the study's cause.

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