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The role of vitamin and mineral deficiencies in rheumatoid arthritis: insights from a comparative study

Ammal Esmaeel Ibrahim[1,*]

[1] Al-Nahrain University. College of Pharmacy, Baghdad, Iraq.

*Corresponding author: Ammal Esmaeel Ibrahim.
Al-Nahrain University. College of Pharmacy, Baghdad, Iraq.
E-mail: dr.ammal.obaidi@nahrainuniv.edu.iq
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Abstract

Introduction: The exact etiology of Rheumatoid arthritis (RA)is unknown, although it occurs due to a complex interplay between genetic, and environmental/ hormonal factors. **Objective:** The aim of this study was to examine for a possible relationship between RA and malnutrition, focusing on vitamins (D, A, B12) and trace elements (zinc, copper). This section will review the potential impact of these limitations on the progress and therapy targeting disease modifying in RA. **Methods**: The study comprised 1500 participants; among which there were 1200 patients diagnosed to be having RA based on the four treatment regimens criteria, i.e., biological therapy, chemotherapy and bio-chemotherapy only (with known disease severity), along with taking of these medications for at least the last three months, while the other set included healthy individuals (n =300). Serum levels of ACPA, vitamins (B, A, and D3), zinc and copper were measured using ELISA kits. **Results:** High ACPA in patients were found compared to the healthy (decreased after treatment, suggesting a relatively lower level), low vitamin D and A concentration, (larger) variations at vit B12, Zn, and Cu compared to controls. Deficiencies in vitamin B12, zinc and copper were significantly corrected by biological agents, chemotherapy, and bio-chemotheraphy while the latter's still higher among RA patients. These findings support the importance of addressing malnutrition, for example by supplementation or diet modification, as part of care in RA to possibly improve treatment response and quality of life. **Conclusion**: Deficiencies and imbalances in nutrients, primarily vitamins, and trace elements are significant in the management and development of RA disease.

Keywords: Rheumatoid arthritis, ACPAs, vitamins, zinc and copper.

Introduction

Rheumatoid arthritis (RA) is systemic autoimmune disease primarily impacting joints. In autoimmune diseases, the body's tissue was harmed as a result of the immune system accidentally attacking it [1-3], in RA, the synovium, the lining of the membranes that surround the joints [4]. It is typically affecting the joint in the hand and feet symmetrically, also it can affect other joints and organs [5], which leads to inflammation, swelling, pain, and eventually can cause damage to the joint tissue and cartilage, the extensive damage to the joints often results in deformities and erosion of bones, which typically leads to significant pain for the patient [5,6]. Although the precise etiology of rheumatoid arthritis is currently unclear, but several elements are believed to be involved, including hormonal, environmental, and genetic [7,8].

Consequences of vitamins deficiencies in RA include neurological symptoms from vitamin B12 deficiency and anemia from folate deficiency, which can worsen fatigue and overall health. Proper RA care not only includes management of inflammation with medications such as disease-modifying anti-rheumatic drugs (DMARDs), but also requires a holistic approach to nutritional deficiencies, that include diet changes, supplements and maintenance nutrition monitoring. This is important in order to optimize treatment outcome and quality of life for patients with RA [9].

The aim of this study was to examine for a

possible relationship between RA and malnutrition, focusing on vitamins (D, A, B12) and trace elements (zinc, copper). This section will review the potential impact of these limitations on the progress and therapy targeting disease modifying in RA.

Methods

Study Design

This study followed the STROBE guidelines (link: https://www.strobe-statement.org/) for cross-sectional study.

Participants and Groups

There were 1500 volunteers in all, divided into five groups for the study. Group A, comprised 300 apparently healthy individuals served as the control group, 4 groups according to the forms of treatment they received; group B-1 consisted of 300 patients newly diagnosed with RA. Group B-2 include 300 patients who received biological treatment, Group B-3 comprised 300 patients who received chemotherapy and Group B-4 involved 300 patients that received bio-chemotherapy.

Ethical Approval

This research was approved from College of Pharmacy, Al-Nahrain University, Baghdad, Iraq (Approval Number: nah.co.pha.H6).

Samples and Analysis

Venous blood samples were collected from all participants to measure serum levels of anti-citrullinated protein autoantibodies (ACPA vitamins (B,A,D3), zinc and copper. Sandwich-ELISA Kits provided by Elabscience, USA, were used to measure these parameters in the serum samples, following the manufacturer's instructions. Measurements were conducted using a Bio-Rad ELISA reader from the UK.

Statistical Analysis

The GraphPad Prism 8 software was used for statistical analysis, and a two-sided $p< 0.05$ was deemed statistically significant.

Results

Table 1. The Mean ±SD for the Parameters.

Parameters	control	patients	bio	chemo	bio chemo	p-value
zinc	99±5.6	56±12	103.41±8.67	110.40±9.12	109.12±10.00	<0.0001
copper	251.5±14	301.00±9.00	255.50±4	250.96±12	256.58±6.5	<0.0001
Vitamin B	687±21.7	5546.9±23.97	808.04±25	820.19±30	915.77±30	<0.0001
Vitamin A	54.89±6.7	124.3±8.6	121.3±12	155.55±9.2	154.29±12	<0.0001
TNF-α	5±0.45	17±2.76	5.5±1.65	4.1±1.12	3.8±0.99	<0.0001
IL β	2.89±0.39	6±1.43	2.3±0.54	2.7±0.43	3.1±1.07	<0.0001
ACPA	9.9±1.76	40±2.9	29±2.67	20±3.40	17±3.2	<0.0001

Source: Own authorship.

Table 2. The correlation between the parameters.

Variables	R value	p- value
Zinc vs TNF-α	−0.81	<0.0001
Zinc vs IL-1β	−0.72	<0.0001
Zinc vs ACPA	−0.55	<0.0001
Copper vs TNF-α	0.67	<0.0001
Copper vs IL-1β	0.75	<0.0001
Vitamin B vs ACPA	−0.64	<0.0001
Vitamin A vs ACPA	0.72	<0.0001
TNF-α vs IL-1β	0.91	<0.0001
TNF-α vs ACPA	0.77	<0.0001

Source: Own authorship.

It was observed that this level significantly decreased in the treatment groups (B2, B-3, and B-4) to 29.3 ± 2.67, 20 ± 2.67, and 17.5 ± 3.2 ng/mL respectively. In comparison, the average level of ACPAs in apparently healthy individuals was within the negative range at 9.9 ± 1.76 ng/mL.

Discussion

Levels of ACPA

The study found that patients newly diagnosed with RA (Group B-1) had a high level of ACPAs of 40.2 ± 3.6 ng/mL. According to the table (1) and table (2) the finding suggest that there is an immune response of rheumatoid arthritis (RA) patients towards citrullinated proteins, which are produced during various processes, including those in the synovial joints **[5]**. Kurowska and co-worker suggest there is a Significance relationship of ACPAs level and diagnosis of RA, they reported the ACPA is a highly specific biomarker for rheumatoid arthritis, and demonstrating that its presence can aid significantly in diagnosing RA, especially in early stages or in atypical cases. ACPA positivity is more specific to RA compared to other markers like rheumatoid factor (RF) **[5]**.

It is found the high level of ACPAs are associated with severity of RA and greater joint damage. Studies suggest that higher ACPA levels correlate with more aggressive disease and a poorer prognosis **[5,7]**.

Vitamins and RA

The relationship between vitamin levels and RA has been the subject of various studies, investigating how deficiencies or imbalances in specific vitamins may influence the onset, progression, and management of RA **[8]**. In this study was include vitamin D, vitamin A, and vitamin B12. Many studies had included that the Iraqi population suffering of vitamin D deficiency **[9-11]**, the results showed that levels of Vitamin D was low in all study's groups, the levels was; 20 ± 2.87, 6 ± 1.5, 15 ± 3.88, 17±5.20, 12 ±3.87, in Group A, Group B1-4 respectively.

Vitamin D is essential for immune system regulation and bone health that regulate immune

responses and controlling inflammation, which can influence RA disease activity. Lower levels of vitamin D have been associated with increased RA severity and activity, and supplementation may give potential advantages for symptom management. research has reported correlation between vitamin D levels and RA. A deficiency in vitamin D might be linked to a higher risk of developing RA.

Data from 29,368 women between the ages of 55 and 69 were examined by Merlino and colleagues in the Iowa Women's Health Study. Their findings suggested that higher vitamin D intake could be associated with a reduced risk of RA. In follow-up study after 11 years, 152 cases of RA were recorded, and an inverse relationship was observed between vitamin D intake and RA risk, using dietary sources and supplements **[10]**.

Many studies have examined the connection between vitamin D levels and RA activity. For instance, Rossini et al, observed an inverse link between vitamin D levels and disease activity in a study consisting from 1,191 RA patients and 1,019 controls **[12]**. Similarly, studies by Welsh, Kerr, Cutolo, and Haque and Bartlett also found that vitamin D deficiency is related to increased RA activity **[13]**. Conversely, other studies did not identify a link between vitamin D deficiency and RA activity. Braun-Moscovici and colleagues, for example, found no correlation between vitamin D levels and disease activity in their study of 85 RA patients.

However, their subjects generally had high disease activity and low D3 levels, which could have impacted the study's results and the lack of correlation. Additionally, Haque and colleagues explored the increased cardiovascular risk in RA patients and found that vitamin D deficiency was associated with cardiometabolic risk factors in RA **[14]**. There is a study indicated that a lack of vitamin D may heighten the risk of autoimmune disorders, including multiple sclerosis, inflammatory bowel disease, Type 1 diabetes, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA). Vitamin D exerts immunoregulatory effects via vitamin D receptors (VDRs) found on antigen-presenting cells, activated T cells, and activated B cells. It appears to influence the immune system by affecting the regulation and differentiation of cells such as lymphocytes, macrophages, and natural killer cells, as well as by modulating cytokine production, The study found a significant negative correlation between serum vitamin D levels and RA disease activity, indicating that lower vitamin D levels were associated with higher disease activity **[14]**.

Consistent results were also reported by Cen et al. where an association was no longer detected within local RA patients when compared with healthy controls **[15]**. RA and Vitamin A Vitamin A is crucial for immune function and cell health, which can affect RA. It's active form, retinoic acid, regulates immune responses and maintains epithelial barriers that are essential in inflammatory diseases such as RA. Vitamin A deficiency has also been suggested to aggravate RA through immune dysregulation or inflammation. Alternatively, sufficient vitamin A levels might be able to suppress inflammation and enhance joint health **[16]**.

Vitamin A influences immune responses. It plays a critical role in maintaining the integrity of mucosal surfaces and regulating immune cell functions **[17]**. Deficiency in vitamin A is linked to increased susceptibility to autoimmune diseases such as, RA **[18]**, the results in this article showed there was a significant difference in Vitamin A level between treatment groups 121.3 ± 9.9, 151.3 ± 155.5 ± 9.2 and control group 165.1 ± 12 in addition the lowest level of vitamin A was reported in RA patients (120.4 ± 8.9), however, the adaptive immune response relies heavily on vitamin A, which, through indirect processes, contributes to the development and proliferation of regulatory T cells as well as other immunological functions **[19]**.

T cell differentiation into regulatory T cells is encouraged by vitamin A's elevation of IL-2 levels. These regulatory T cells are crucial for preventing autoimmune reactions. They also play a role in modulating transforming growth factor-β (TGF-β), a significant factor in immune and inflammatory responses, with retinoic acid influencing its expression **[20]**. Without this regulatory process, TGF-β alone could trigger autoimmune responses, this suggests the role of vitamin A in autoimmune diseases **[21]**. This study highlights the potential links between vitamin A complex and RA, emphasizing the need for further research to validate these findings.

Vitamin B12 deficiency is frequently observed in patients with rheumatic diseases, recent evidence suggests that autoimmune-related vitamin B12 deficiencies may extend beyond this condition. The symptoms of low vitamin B12 levels can often be misleading, as they overlap with those of various rheumatic diseases. Common symptoms such as neuropsychiatric issues, anemia, and fatigue are frequently mistaken for manifestations of the rheumatic disease itself, leading to a lack of further evaluation, as shown in Table 1, the RA patients was suffering of Vitamin B12 deficiency (554.69 ± 23.97) but in treatment groups noticed that level of vitamin B reach to optimal level (808.03 ±75, 820.19 ± 30 and 915.76 ± 79) in B-2, B-3 respectively.

Furthermore, reported level of vitamin B was 687

± 21 in the group A. Statistically, a significant difference in vitamin B level between group B-1 and B 2-4 groups, but we did not find a significant difference between B-2 and B-3 study groups but not with B-4 group. This study showed that the vitamins supplements with treatments are important in order to management the RA disease. Vitamin B is important for protein metabolism and neurotransmitter production. It is known for its potential to reduce inflammation, which can benefit RA patients. Research indicates that sufficient levels of B6 may reduce inflammation and joint pain related to RA. Intake of higher amounts of B6 is associated with lower disease activity in patients with RA **[22]**.

Another study describes the anti-inflammatory Role of Vitamin B; an important role plays vitamin for protein metabolism and production of neurotransmitter. It is famed for its anti-inflammatory properties, which could be good news for those with RA. indicate that high levels of B may reduce inflammation and joint pain in patients with RA. Higher B intake is associated with lower disease activity in patients with RA according to research. Then there's vitamin B, which your body needs to build a new DNA and repair old ones. It's frequently used to offset the side effects of RA drugs such as methotrexate, which can lower levels of vitamin B. Vitamin B supplement therapy may enhance the efficacy of, and reduce drug side effects in, RA disease-modifying agents. There is evidence to suggest that as an adjunct treatment, vitamin B supplementation may improve response and reduced disease progression **[23]**.

Zinc

Zinc, an essential trace element, takes a part in a number of biologic processes including protein synthesis, cellular growth and immunologic function. It is crucial for the growth and function of immune cells, a deficiency can lead to impaired immunity that even worsens autoimmune conditions such as RA, patients with RA frequently present with low level of serum zinc may be due to increased inflammatory activity and disturbed zinc metabolism **[24]**, in current study had showed significant difference between Group A and group B-1 at mean concentration (65 ± 12, 99 ± 5.6) respectively. Whereas, the zinc content in RA patients of treatment groups (B-2, 103.42 ±8.67, B-3 110.40±9.12 and B-4 109.12±10.12) was within normal limits. The finding demonstrated a decreased level of zinc in the sera of patients with rheumatoid arthritis compared to healthy subjects. This is consistent with the previous reports **[25-27]**.

Patients with RA often exhibit low serum levels of zinc, which might be related to increased inflammatory activity and altered zinc metabolism **[28]**. Research has shown that zinc deficiency can contribute to disease severity by impairing the immune system and increasing oxidative stress **[24,28,29]**. Several studies have investigated the effects of zinc supplementation on RA. According to several studies, zinc may help reduce the symptoms of RA by acting as an antioxidant and anti-inflammatory. Zinc supplementation decreased clinical symptoms and inflammatory markers in RA patients, according to a study by Zheng et al., which may help ease some of the symptoms of the condition. In a chick model, long-term zinc deficiency led to a reduction of pro-inflammatory cytokines expression, such as, IL-1β, IL-6 and TNF, that crucial in the development of RA. Increasing zinc intake raised zinc level in plasma and reduced CRP and IL-6 concentrations compared to a placebo. Zinc is essential for the immune system, influencing both innate and adaptive immune cells, though there is a strong link between blood zinc levels and RA disease activity **[29]**.

The results in this study in Table 1 agreed with study that reported that the level of copper significantly higher that healthy group, the level of copper was 301.01 ±9.01 in B1 GROUP and 120 ± 7.9 in group A. The level of Copper in RA treatment groups also was higher than healthy group 251.5 ±14, 250.96 ±12 and 265.58 ±12.65 in B-2, B-3 and B-4 respectively but lower B-1 group. This finding consistent with the results of Xin et al., whose meta-analysis indicated that patients with RA typically have elevated serum copper levels and reduced serum zinc levels which agreed with our results between the Copper and Zinc level in this study. This could be explained through the antagonistic interaction between copper and zinc **[24]**.

Excessive intake one of them lead to impair absorption second one. Another study found a strong positive relationship between RA patients' morning stiffness, erythrocyte sedimentation rate, and serum copper levels. This suggests that serum copper levels could serve as a potential biomarker for disease activity in RA. Generally, RA patients exhibit elevated blood copper levels. A heavy metal chelator called D-penicillamine is used to treat RA. D-penicillamine is thought to chelate copper ions, which could prevent cell development. By promoting Fas-mediated apoptosis. The results in this study in Table 1 agreed with study that reported that the level of copper significantly higher that healthy group, the level of copper was 301.01 ±9.01 in B-1 GROUP and 120 ± 7.9 in group A. The level of Copper in RA treatment groups also was higher than healthy group 251.5 ±14, 250.96 ±12 and 265.58 ±12.65 in B-2, B-3 and B-4 respectively but lower B-1 group.

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Conclusion

The study concludes that nutritional deficiencies and imbalances, particularly in vitamins D, A, B12, and trace elements like zinc and copper, play a significant role in the management and progression of rheumatoid arthritis. Elevated levels of anti-citrullinated protein antibodies (ACPAs) in patients with rheumatoid arthritis were reduced with treatment, indicating a potential link between disease activity and nutritional status. It was observed significant differences in blood levels of zinc, copper, and vitamins A, B and D between patients with RA and healthy individuals.

CRediT

Author contributions: Conceptualization, methodology, investigation, data collection, formal analysis, data interpretation, supervision, writing—original draft: Ammal Esmaeel Ibrahim.

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Ethical Approval

This research was approved from College of Pharmacy, Al-Nahrain University, Baghdad, Iraq (Approval Number: nah.co.pha.H6).

Informed Consent

Informed consent was obtained from all participants involved in the study, with all procedures explained in detail before participation.

Funding

Not applicable.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request, and all data is stored following privacy and ethical guidelines.

Conflict of Interest

The authors declare no competing interests.

Similarity Check

It was applied by Ithenticate[@].

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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