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RESEARCH ARTICLE

STUDY OF SERUM CALCIUM, PHOSPHORUS, IRON AND MAGNESIUM LEVELS IN THE RHEUMATOID ARTHRITIS PATIENTS

Deepak kumar Jat[1], Dr. Sushma BJ[2,*], Dr. Gaffar Khan[3] and Dr. Mukesh Tiwari[4]

[1]PG Medical Biochemistry, Department of Biochemistry, National Institute of Medical Sciences & Research, Jaipur; [2]Professor & Head, Department of Biochemistry, National Institute of Medical Sciences & Research, Jaipur; [3]Assistant Professor, Department of Orthopaedics, National Institute of Medical Sciences & Research, Jaipur; [4]Professor, Department of Orthopaedics, Dean / Principal & Controller, National Institute of Medical Sciences & Research, Jaipur

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***Corresponding author:**
Dr. Sushma BJ

ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by systemic inflammation and joint damage. Variations in calcium, phosphorus, iron, and magnesium levels may influence disease progression, but previous studies report mixed findings. Evaluating these mineral levels and their ratios in RA patients and healthy controls may offer valuable clinical insights. **Objectives:** To determine and compare the serum calcium, phosphorus, iron and magnesium levels in patients with Rheumatoid Arthritis and Healthy Controls. To asses serum calcium and phosphorus ratio in patients with Rheumatoid Arthritis. **Materials and Methods:** This cross-sectional study includes 106 subjects, with 53 Rheumatoid Arthritis patients and 53 Healthy Controls, aged 30 to 70 years. Clinically stable RA patients are included, while those with osteoarthritis, autoimmune disorders, severe illnesses, chronic inflammation, recent RA medication changes, or mineral supplements are excluded. Serum calcium, phosphorus, iron, and magnesium levels, along with the calcium-to-phosphorus ratio, are analyzed using biochemical assays and statistical methods. **Results:** RA patients have significantly lower calcium, magnesium, and iron levels but higher phosphorus levels compared to healthy controls. The calcium-to-phosphorus ratio is notably reduced in RA patients. **Conclusion:** RA patients exhibit significantly lower serum calcium ($p = 0.01632$), magnesium ($p = 0.00536$), and iron ($p < 0.0001$) levels but higher phosphorus levels ($p = 0.00509$) compared to healthy controls. The calcium-to-phosphorus ratio is significantly reduced ($p < 0.0001$), indicating impaired bone mineralization and an increased risk of fractures.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that primarily affects the synovial joints, causing inflammation, cartilage destruction, and bone erosion. It leads to pain, stiffness, joint deformities, and reduced quality of life.[1,20] RA causes symmetric joint inflammation, starting in small joints and progressing to larger ones. RA patients have an increased risk of atherosclerosis and cardiovascular diseases (CVD).[2] RA causes progressive joint damage and deformities, leading to chronic pain and disability. It also increases the risk of osteoporosis and fractures due to impaired bone metabolism.[3] Environmental and developmental factors influence RA progression. Smoking worsens disease severity, while infections, pollution, and hormonal fluctuations contribute to chronic inflammation.[4] Rheumatoid arthritis (RA) affects 1–2% of the global population, causing disability and reducing quality of life. It is three times more common in women and usually develops between ages 30 and 60. In India, its prevalence is around 0.75%, highlighting the need for better diagnosis and treatment. RA is more common in developed regions, while in developing countries, limited healthcare access and delayed diagnosis worsen its impact, especially in rural areas.[5,6,7] RA-associated systemic inflammation disrupts mineral homeostasis, increasing disease severity. It impairs calcium absorption, promotes renal excretion, and alters the calcium-phosphorus balance, leading to accelerated bone loss.[8,9]

Calcium (Ca): Calcium is the most abundant cation in the body and a key component of hydroxyapatite, essential for bone density, nerve function, muscle contraction, and blood coagulation.[10,11]

Phosphorus (P): Phosphorus, present in both organic and inorganic forms, plays a crucial role in ATP production, nucleic acid synthesis, and maintaining the calcium-phosphorus ratio necessary for bone formation.[12]

Magnesium (Mg): Magnesium is involved in over 300 enzymatic reactions, including energy production and

inflammatory regulation. It activates vitamin D and serves as a cofactor in ATP-dependent processes[1011]. Magnesium deficiency is linked to elevated inflammatory markers such as CRP and ESR, increasing oxidative stress and inflammation in RA.[13,14,15]

Iron (Fe): Iron is vital for oxygen transport and enzyme function but can contribute to oxidative stress and inflammation when excessive, leading to tissue damage.[16,17] Iron dysregulation, influenced by increased hepcidin levels, reduces iron availability, contributing to anemia of chronic disease. Excess iron further promotes oxidative stress, exacerbating joint damage.[18,19]

OBJECTIVES

- To determine and compare the serum calcium, phosphorus, iron and magnesium levels in patients with Rheumatoid Arthritis and Healthy Controls.
- To asses serum calcium and phosphorus ratio in patients with Rheumatoid Arthritis.

MATERIALS AND METHODS

Source of data and study design: It is a comparative cross Sectional study, conducted at the National Institute of Medical Sciences & Hospital (NIMS Hospital), Jaipur (Rajasthan) in the Department of Biochemistry in association with the Department of Orthopaedics and General Medicine. Samples were analyzed for biochemical investigations in the Department of Biochemistry, National Institute of Medical Sciences & Research (NIMS&R) and NIMS Hospital, Jaipur.

Inclusion Criteria

- Subjects in the Age group 30-70 years of all genders and Healthy Controls.
- Clinically diagnosed stable Rheumatoid Arthritis patients.
- Subjects willing to give informed consent.

Exclusion Criteria: The following patients were excluded from the study.

- Patients with osteoarthritis.
- Patients on magnesium, calcium, phosphorus and iron supplements.
- Patients with other autoimmune disorders.
- Patients with severe unrelated medical conditions.
- Pregnant and lactating women.
- Patients with recent changes in Rheumatoid Arthritis (RA) medication.
- Patients with other chronic inflammation.

Sample collection: A 3ml fasting venous blood sample will be taken from patients in plain vial and subjected to centrifuge for serum separation and will be used for estimation the tests at the Central Biochemistry Laboratory at NIMS college where serum calcium, phosphorus, magnesium and iron levels Rheumatoid Arthritis and Healthy Controls measured.

RESULTS

A total number of 106 subjects were included in the study. This includes 53 subjects of controls group and 53 subjects of case group of RA of age group of 30-70 years. Table No. 1 shows the descriptive statistics for calcium, phosphorus, magnesium, and iron levels in both the Controls and Rheumatoid Arthritis (RA) groups.

Controls Group: Calcium ranges from 6.5 to 11.9 mg/dL, with a median (IQR) of 8.7 (8.1–9.4) and a mean ± SD of 8.86 ± 1.13. Phosphorus varies from 2.2 to 7.7 mg/dL, with a median (IQR) of 4 (3.5–4.4) and a mean ± SD of 4.07 ± 1.15. Magnesium falls between 0.5 and 3.4 mg/dL, with a median (IQR) of 1.9 (1.2–2.2) and a mean ± SD of 1.76 ± 0.68. Iron ranges from 10 to 153 µg/dl, with a median (IQR) of 64 (38–89) and a mean ± SD of 65.92 ± 34.97. Calcium/Phosphorus ratio spans from 0.974 to 4.21, with a median (IQR) of 2.29 (1.83–2.71) and a mean ± SD of 2.34 ± 0.68

Rheumatoid Arthritis Group: Calcium ranges from 5.4 to 10.9 mg/dL, with a median (IQR) of 8.2 (7.5–9) and a mean ± SD of 8.33 ± 1.11. Phosphorus falls between 2.1 and 7.7 mg/dL, with a median (IQR) of 4.9 (3.9–5.8) and a mean ± SD of 4.77 ± 1.36. Magnesium varies from 0.5 to 2.3 mg/dL, with a median (IQR) of 1.6 (0.88–2.0) and a mean ± SD of 1.41 ± 0.59. Iron ranges from 10 to 102 µg/dl, with a median (IQR) of 23 (16–40) and a mean ± SD of 33.94 ± 26.16. Calcium/Phosphorus ratio spans from 0.974 to 3.6, with a median (IQR) of 1.71 (1.36–2.16) and a mean ± SD of 1.92 ± 0.69. Table No. 2 shows a comparative analysis of calcium, phosphorous, magnesium, and iron levels between the Controls and Rheumatoid Arthritis (RA) groups, utilizing the t-test to determine statistical significance.

The mean calcium level was significantly lower in Rheumatoid Arthritis patients (8.33 ± 1.11 mg/dL) compared to the control group (8.86 ± 1.13 mg/dL) with a significant difference (t-test = 2.441, p = 0.01632). Phosphorus levels were significantly higher in the Rheumatoid Arthritis group (4.77 ± 1.36 mg/dL) compared to the Controls group (4.07 ± 1.15 mg/dL) with a significant difference (t-test = -2.862, p = 0.00509). Magnesium levels were significantly lower in Rheumatoid Arthritis patients (1.41 ± 0.59 mg/dL) compared to the Controls group (1.76 ± 0.68 mg/dL) with a significant difference (t-test = 2.844, p = 0.00536). Iron levels were also significantly lower in the Rheumatoid Arthritis group (33.94 ± 26.16 µg/dl) compared to the Controls group (65.92 ± 34.97 µg/dl) with a highly significant difference (t-test = 5.331, p < 0.0001). Additionally, the calcium/phosphorus ratio was significantly lower in Rheumatoid Arthritis patients (1.92 ± 0.69) compared to the Controls group (2.34 ± 0.68) with a highly significant difference (t-test = 5.410, p < 0.0001).
Table No. 3 shows the frequency distribution of the calcium/Phosphorus (Ca/P) ratio among patients in the Controls and Rheumatoid Arthritis (RA) groups.

Calcium/Phosphorus Ratio Distribution:
0.0 - 1.00:
Controls Group: 1 (1.89%)
Rheumatoid Arthritis Group: 2 (3.77%)
1.01 - 2.00:
Controls Group: 17 (32.08%)
Rheumatoid Arthritis Group: 33 (62.26%)
2.01 - 3.00:
Controls Group: 28 (52.83%)
Rheumatoid Arthritis Group: 13 (24.53%)
3.01 - 4.00:
Controls Group: 6 (11.32%)

Table 1. Descriptive statistics of calcium, phosphorous, magnesium and iron levels of patients of Controls and Rheumatoid Arthritis groups

Variables		Minimum	Maximum	Median (IQR)	Mean ± SD
Controls Group	Calcium	6.5	11.9	8.7 (8.1-9.4)	8.86 ± 1.13
	Phosphorous	2.2	7.7	4 (3.5-4.4)	4.07 ± 1.15
	Magnesium	0.5	3.4	1.9 (1.2-2.2)	1.76 ± 0.68
	Iron	10	153	64 (38-89)	65.92 ± 34.97
	Calcium/Phosphorous	0.974	4.21	2.29 (1.83-2.71)	2.34 ± 0.68
Rheumatoid Arthritis Group	Calcium	5.4	10.9	8.2 (7.5-9)	8.33 ± 1.11
	Phosphorous	2.1	7.7	4.9 (3.9-5.8)	4.77 ± 1.36
	Magnesium	0.5	2.3	1.6 (0.88-2.0)	1.41 ± 0.59
	Iron	10	102	23 (16-40)	33.94 ± 26.16
	Calcium/Phosphorous	0.974	3.6	1.71 (1.36-2.16)	1.92 ± 0.69

Table 2. Comparing calcium, phosphorous, magnesium and iron levels between Controls and Rheumatoid Arthritis group of patients by using t-test

Variables	Controls	Rheumatoid Arthritis	t-test	P - Value	Significance
Calcium	8.86 ± 1.13	8.33 ± 1.11	2.441	0.01632	All are Significant
Phosphorous	4.07 ± 1.15	4.77 ± 1.36	-2.862	0.00509	
Magnesium	1.76 ± 0.68	1.41 ± 0.59	2.844	0.00536	
Iron	65.92 ± 34.97	33.94 ± 26.16	5.331	< 0.0001	
Calcium/Phosphorous	2.34 ± 0.68	1.92 ± 0.69	5.410	< 0.0001	

Table 3. Frequency distribution of calcium/Phosphorus ratio of patients

Calcium/Phosphorus ratio	Controls Group		Rheumatoid Arthritis	
	n = 53	In %	n = 53	In %
0.0 - 1.00	1	1.89%	2	3.77%
1.01 - 2.00	17	32.08%	33	62.26%
2.01 - 3.00	28	52.83%	13	24.53%
3.01 - 4.00	6	11.32%	5	9.43%
4.01 - 5.00	1	1.89%	0	0.00%

Rheumatoid Arthritis Group: 5 (9.43%)
4.01 - 5.00:
Controls Group: 1 (1.89%)
Rheumatoid Arthritis Group: 0 (0.00%)

DISCUSSION

The present study was conducted in the Department of Biochemistry, in association with the Department of Orthopaedics & General Medicine, national institute of Medical Sciences & Research, Jaipur (Rajasthan). The study included a total of 106 subjects, who were divided into 53 normal controls and 53 with case subjects at the National Institute of Medical Sciences & Research, Jaipur, Rajasthan, India.

Serum Calcium: Serum calcium levels are significantly lower in RA patients compared to the control group. Gough *et al*. (1994) report that reduced calcium levels in RA are associated with bone mineral density (BMD) loss, increasing the risk of fractures. Chronic inflammation and excessive cytokine activity, particularly TNF-α and IL-6, stimulate osteoclast function while suppressing osteoblast activity, leading to accelerated bone resorption (Haugeberg *et al*., 2000). Additionally, long-term glucocorticoid therapy, commonly used in RA management, further disrupts calcium homeostasis by reducing intestinal absorption and increasing renal excretion (Dixon *et al*., 2006). These findings reinforce the role of calcium deficiency in bone-related complications in RA patients.

Serum Phosphorus: RA patients exhibit significantly higher phosphorus levels than controls, suggesting altered phosphorus metabolism. A substantial proportion of RA patients have phosphorus levels exceeding 5.0 mg/dL, which may contribute to joint damage and bone resorption (Mohammed *et al*., 2020). Long-term corticosteroid therapy can affect phosphorus homeostasis by influencing renal phosphate handling, further exacerbating bone loss (Laan *et al*., 1993). Verheij *et al*. **(2000)** indicate that phosphorus levels vary with disease severity, with elevated levels in early RA due to increased bone turnover, while chronic inflammation and prolonged medication use in advanced RA contribute to phosphorus depletion. Bijlsma *et al*. (2002) suggest that vitamin D deficiency, common in RA patients, further disrupts phosphorus metabolism, affecting overall bone health.

Serum Magnesium: Magnesium levels are significantly lower in RA patients, indicating a potential link between magnesium deficiency and inflammatory processes. Zeng *et al*. (2015) report that low magnesium levels correlate with increased inflammatory markers such as TNF-α and IL-1β**,** exacerbating systemic inflammation. Magnesium plays a crucial role in immune regulation and bone metabolism, and its deficiency may accelerate disease progression. Nielsen *et al*. (2004) highlight that inadequate magnesium levels can impair immune function, increase oxidative stress, and intensify joint inflammation. Cuciureanu and Vink (2011) further demonstrate that RA patients with magnesium deficiency experience more severe joint pain, stiffness, and fatigue. Additionally, magnesium deficiency negatively affects cartilage integrity and accelerates joint degradation, as observed by Castiglioni *et al*. (2013) and de Souza *et al*. (2018)**.** These findings suggest that monitoring and correcting magnesium deficiency may help in RA management. Serum Iron: RA patients exhibit significantly lower iron levels than controls, which aligns with the high prevalence of anemia in RA. Weiss and Goodnough (2005) explain that inflammatory cytokines, particularly IL-6**,** impair iron metabolism by

upregulating hepcidin, a hormone that blocks iron release from storage sites, leading to functional iron deficiency. Vreugdenhil *et al*. (1990) report that RA patients often suffer from reduced dietary iron absorption and increased iron retention in the reticuloendothelial system, further contributing to anemia. Peeters *et al*. (1996) establish a direct association between iron deficiency and inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR**)**, indicating that iron deficiency may correlate with disease severity**.** Krause *et al*. (2013) emphasize that anemia in RA patients negatively affects physical function, increases fatigue, and reduces overall quality of life. Addressing iron deficiency through supplementation, dietary adjustments, and effective anti-inflammatory treatment may improve patient outcomes **(**Pinto *et al*., 2018**).**

Calcium-to-Phosphorus Ratio (Ca/P Ratio): This study finds a significantly lower Ca/P ratio in RA patients, which may contribute to bone demineralization and increased fracture risk. Spector *et al*. (1993) report that an altered Ca/P ratio disrupts bone homeostasis, leading to impaired bone mineralization and structural weakness. Chronic inflammation accelerates bone loss, further reducing the Ca/P ratio. Gómez-Vaquero *et al*. (2007) highlight that phosphorus dysregulation in RA contributes to abnormal bone turnover, increasing osteoporosis susceptibility. Cutolo *et al*. (2014) emphasize that prolonged inflammation, combined with calcium depletion, negatively impacts bone strength, raising the likelihood of fractures. In the investigation, the analysis of serum calcium, phosphorus, magnesium, and iron in RA revealed noteworthy patterns, shedding light on the association compare serum calcium, phosphorus, magnesium and iron levels.

CONCLUSION

In the present study, we found altered RA parameters (Serum calcium, phosphorus, magnesium, and iron) in subjects with RA as compared to the Controls and case subjects. This study demonstrates significant mineral imbalances in rheumatoid arthritis (RA) patients. Serum calcium levels are markedly lower ($p = 0.01632$), increasing the risk of bone complications due to chronic inflammation and steroid use. Phosphorus levels are significantly higher ($p = 0.00509$), contributing to joint damage and bone resorption. Magnesium deficiency ($p = 0.00536$) is linked to increased inflammation and joint deterioration. Iron levels are significantly reduced ($p < 0.0001$), leading to anemia and worsening disease severity. Additionally, the calcium-to-phosphorus (Ca/P) ratio is significantly lower ($p < 0.0001$), indicating impaired bone mineralization and a higher fracture risk. These findings highlight the need for early monitoring and targeted interventions to improve bone health and overall disease management in RA patients. Our study suggests that all RA patients should undergo regular monitoring of mineral levels to improve disease management and prevent complications.

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