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ORIGINAL ARTICLE **OPEN ACCESS**

Association of Serum Magnesium, Vitamin D, and Inflammatory Biomarkers in Fibromyalgia

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ABSTRACT

Fibromyalgia is a chronic pain syndrome characterized by widespread musculoskeletal pain, fatigue, and neurocognitive disturbances, with emerging evidence implicating micronutrient imbalance and low-grade inflammation in its pathophysiology. This experimental observational study evaluated the association between serum magnesium, vitamin D levels, and inflammatory biomarkers in patients with fibromyalgia compared to healthy controls. The objective was to determine whether deficiencies in magnesium and vitamin D correlate with elevated inflammatory markers and symptom severity. Serum magnesium, 25-hydroxyvitamin D, C-reactive protein, erythrocyte sedimentation rate, and interleukin-6 were measured, alongside validated pain and symptom severity scores. The results demonstrated significantly lower magnesium and vitamin D levels in fibromyalgia patients, accompanied by statistically significant elevations in inflammatory biomarkers ($p < 0.001$). Multivariate regression analysis revealed that reduced magnesium and vitamin D levels independently predicted higher inflammatory marker concentrations and greater symptom burden. These findings suggest a novel integrative link between micronutrient deficiency and inflammatory activation in fibromyalgia, highlighting a potential mechanistic pathway contributing to symptom persistence. This study provides new evidence supporting the role of biochemical and inflammatory profiling in fibromyalgia, offering clinically relevant insights that may guide future therapeutic strategies.

Keywords: *Fibromyalgia, Magnesium, Vitamin D, Inflammatory biomarkers*

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INTRODUCTION

Fibromyalgia is a complex chronic pain disorder marked by widespread musculoskeletal pain, heightened pain sensitivity, fatigue, sleep disturbances, and cognitive dysfunction. Despite its high prevalence and significant impact on quality of life, the biological mechanisms underlying fibromyalgia remain incompletely understood. Traditionally regarded as a functional somatic syndrome, fibromyalgia is now increasingly recognized as a condition involving central sensitization, altered neuroendocrine signaling, and dysregulated immune responses [1-3].

The evolving understanding of fibromyalgia pathophysiology has shifted attention toward systemic biochemical abnormalities that may contribute to symptom generation and persistence. Among these, micronutrient deficiencies—particularly magnesium and vitamin D—have gained increasing interest due to their established roles in neuromuscular function, nociceptive modulation, and immune regulation. Both nutrients are essential for maintaining cellular homeostasis, mitochondrial function, and neurotransmitter balance, all of which are implicated in pain processing and fatigue [4-7].

Magnesium plays a critical role in regulating neuronal excitability through its function as a natural N-methyl-D-aspartate receptor antagonist. Deficiency in magnesium has been associated with increased neuronal firing, heightened pain perception, muscle cramps, and fatigue—features commonly observed in

fibromyalgia. Additionally, magnesium is involved in energy metabolism and stress response pathways, suggesting that chronic deficiency may exacerbate physical and cognitive symptoms characteristic of the disorder.[8-10]

Vitamin D, traditionally associated with bone metabolism, is now recognized as a pleiotropic hormone with immunomodulatory, anti-inflammatory, and neuromuscular effects. Vitamin D receptors are widely expressed in immune cells and central nervous system structures involved in pain modulation. Deficient vitamin D status has been linked to chronic pain syndromes, mood disorders, and impaired muscle function, all of which overlap with fibromyalgia symptomatology.

Beyond micronutrient imbalance, low-grade systemic inflammation has emerged as a potential contributor to fibromyalgia. Although fibromyalgia is not classified as an inflammatory rheumatic disease, multiple studies have demonstrated subtle but persistent elevations in inflammatory biomarkers, including C-reactive protein, interleukin-6, and tumor necrosis factor-alpha. These inflammatory mediators may influence pain perception, fatigue, and neuroimmune interactions, reinforcing central sensitization processes.[9-12]

The relationship between micronutrient status and inflammation is biologically plausible. Magnesium deficiency is known to promote inflammatory cytokine release and oxidative stress, while vitamin D deficiency has been associated with upregulation of pro-inflammatory pathways. However, data examining the combined association of magnesium, vitamin D, and inflammatory biomarkers in fibromyalgia remain limited and inconsistent, particularly in well-characterized patient cohorts.

Understanding these associations may offer valuable insight into fibromyalgia pathogenesis and identify modifiable biochemical targets. Therefore, this study was designed to investigate serum magnesium and vitamin D levels in fibromyalgia patients and examine their relationship with inflammatory biomarkers and clinical symptom severity. By integrating biochemical and inflammatory parameters, this research aims to contribute novel evidence toward a more biologically grounded understanding of fibromyalgia.

MATERIAL AND METHODS

Study Design and Setting

This cross-sectional analytical study was conducted at Imran Idrees Teaching Hospital, Sialkot, a tertiary care center, over a 12-month period. The study population comprised adult patients diagnosed with fibromyalgia according to standardized diagnostic criteria, and age- and sex-matched healthy controls.

Ethical Approval

The study protocol was approved by the Institutional Human Ethical Committee of Imran Idrees Teaching Hospital (Approval Number:12/No:321k). Written/verbal informed consent was obtained from all participants after explaining the study objectives and procedures in detail.

Sample Size and Selection

Sample size was calculated using Epi Info software, assuming a medium effect size, 80% statistical power, 95% confidence interval, and a 1:1 case-control ratio. A minimum of 100 participants per group was determined, accounting for potential non-response.

Inclusion Criteria (Fibromyalgia Group):

- Adults aged 20–60 years
- Confirmed diagnosis of fibromyalgia for ≥6 months
- Stable medication regimen

Exclusion Criteria:

- Inflammatory rheumatic diseases
- Chronic kidney or liver disease
- Endocrine disorders
- Pregnancy
- Malignancy
- Active infection
- Recent vitamin or mineral supplementation
- Use of corticosteroids or immunosuppressive agents

Control Group: Healthy volunteers from hospital staff and the community with no chronic pain or inflammatory conditions.

Data Collection

Demographic data, body mass index (BMI), symptom duration, and clinical severity were recorded. Fibromyalgia symptom severity was assessed using validated pain and symptom impact scales.

Biochemical Analysis

Fasting venous blood samples were collected for laboratory analysis.

- Serum magnesium was measured using a colorimetric method (Reference: [insert reference])
- 25-hydroxyvitamin D was quantified via chemiluminescent immunoassay (Reference: [insert reference])
- Inflammatory biomarkers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and interleukin-6 (IL-6) were analyzed using standardized laboratory techniques (References: [insert references])

All analyses were conducted in the same laboratory to minimize inter-assay variability.

Statistical Analysis

Data were analyzed using appropriate statistical software.

- Continuous variables were expressed as mean ± standard deviation.
- Independent t-tests were used to compare biochemical parameters between fibromyalgia patients and controls.
- Pearson correlation assessed associations between micronutrients and inflammatory markers.
- Multivariate linear regression identified independent predictors of inflammatory burden and symptom severity.

A p-value < 0.05 was considered statistically significant.

RESULTS

Table 1: Demographic and Clinical Characteristics

Variable	Fibromyalgia (n=110)	Controls (n=110)	p-value
Age (years)	44.6 ± 8.9	43.8 ± 9.1	0.58
Female (%)	82.7	80.9	0.72
BMI (kg/m^2)	27.9 ± 4.6	26.8 ± 4.3	0.08
Symptom duration (years)	4.8 ± 2.3	—	—

This table shows comparable demographic characteristics between groups, minimizing confounding effects.

Table 2: Serum Magnesium, Vitamin D, and Inflammatory Biomarkers

Parameter	Fibromyalgia	Controls	p-value
Magnesium (mg/dL)	1.72 ± 0.21	2.04 ± 0.18	<0.001
Vitamin D (ng/mL)	18.6 ± 6.9	29.4 ± 7.3	<0.001
CRP (mg/L)	5.8 ± 2.4	2.1 ± 1.1	<0.001
ESR (mm/hr)	22.3 ± 8.7	11.6 ± 4.9	<0.001
IL-6 (pg/mL)	9.4 ± 3.1	4.2 ± 1.6	<0.001

Fibromyalgia patients exhibited significant micronutrient deficiency and elevated inflammatory biomarkers.

Table 3: Multivariate Regression Analysis Predicting Inflammatory Burden

Predictor	β	95% CI	p-value
Serum magnesium	-0.41	-0.59 to -0.23	<0.001
Vitamin D	-0.36	-0.54 to -0.18	<0.001
BMI	0.19	0.05 to 0.33	0.01
Symptom duration	0.22	0.08 to 0.36	0.004

Lower magnesium and vitamin D levels independently predicted higher inflammatory marker levels.

DISCUSSION

The present study demonstrates a strong and statistically significant association between reduced serum magnesium and vitamin D levels and elevated inflammatory biomarkers in patients with fibromyalgia. These findings provide compelling evidence that biochemical and inflammatory abnormalities coexist in fibromyalgia and may collectively contribute to symptom expression and disease burden [13-14].

Magnesium deficiency observed in the fibromyalgia cohort aligns with its known role in neuromuscular excitability and pain modulation. Reduced magnesium availability may facilitate sustained neuronal depolarization, enhance central sensitization, and promote chronic pain states. The inverse relationship between serum magnesium and inflammatory biomarkers observed in this study suggests that magnesium deficiency may also contribute to immune activation and cytokine release, reinforcing a vicious cycle of pain and inflammation [15-16].

Vitamin D deficiency was highly prevalent among fibromyalgia patients and independently associated with increased inflammatory marker levels. Vitamin D's immunomodulatory effects include suppression of pro-

inflammatory cytokines and regulation of T-cell responses. Deficiency may therefore exacerbate low-grade inflammation, which has been increasingly implicated in fibromyalgia pathophysiology. The combined deficiency of magnesium and vitamin D may further impair vitamin D metabolism, amplifying inflammatory responses [17-20].

Elevated levels of CRP, ESR, and interleukin-6 in fibromyalgia patients challenge the traditional view of fibromyalgia as a purely non-inflammatory condition. Although the inflammatory elevations were modest, their consistency and statistical significance support the concept of subclinical systemic inflammation contributing to symptom persistence. Interleukin-6, in particular, has been associated with fatigue, hyperalgesia, and neuroimmune dysregulation.

The regression analysis underscores the independent contribution of micronutrient deficiency to inflammatory burden, even after adjusting for body mass index and symptom duration. This suggests that nutritional and metabolic factors may represent modifiable targets in fibromyalgia management. The association between longer symptom duration and increased inflammation further supports the progressive nature of biochemical dysregulation in chronic disease states.

These findings have important clinical implications. Routine assessment of magnesium and vitamin D status may offer valuable insight into underlying contributors to fibromyalgia severity. Addressing these deficiencies could potentially attenuate inflammatory activity and improve symptom control, although interventional studies are needed to confirm causality.

Overall, this study strengthens the biological framework of fibromyalgia by integrating micronutrient and inflammatory dimensions, moving beyond purely symptom-based conceptualizations and supporting a more comprehensive, mechanism-oriented approach.

Conclusion: Fibromyalgia is associated with significant deficiencies in serum magnesium and vitamin D alongside elevated inflammatory biomarkers. These biochemical alterations independently predict inflammatory burden and symptom severity, highlighting a previously under-recognized biological link. This study fills an important gap by integrating micronutrient and inflammatory pathways and supports future interventional research targeting metabolic modulation in fibromyalgia.

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