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Serum Uric Acid Levels in Multiple Sclerosis: A Case Control Study

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Abstract

Background: Oxidative stress contributes to multiple sclerosis (MS) pathogenesis, and serum uric acid (SUA) is a potent endogenous antioxidant. Serum uric acid (SUA), have therefore become a topic of scientific interest due to their potential modulatory role in CNS injury including multiple sclerosis.
Methods: In this case–control study, 44 patients with MS and 44 age- and sexmatched healthy controls were evaluated. SUA levels were measured using enzymatic methods. Associations between SUA levels and demographic variables, disability (Expanded Disability Status Scale, EDSS), disease duration, ambulation status, and disease-modifying therapies (DMTs) were analyzed using ANOVA and regression models adjusted for age, sex, and renal function.
Results: MS patients exhibited significantly lower SUA levels compared to healthy controls ($p < 0.05$). SUA levels were not significantly associated with EDSS scores, disease duration, or ambulation status. While DMT exposure influenced SUA levels overall, no significant pairwise differences were observed between specific drugs.
Conclusion: These findings support the potential utility of SUA as a diagnostic biomarker in MS and as a marker of treatment response to DMTs. However, SUA levels do not correlate with disease duration or physical disability (EDSS).

Keywords:

Uric acid, Multiple sclerosis, Disease modifying therapies.
SUA: S. Uric Acid, MS: Multiple Sclerosis, DMTs: Disease Modifying Therapies**,** EDSS: Expanded Disability Status Scale

1. Introduction

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disorder of stress are key contributors to MS pathogenesis, acting through mechanisms such as peroxynitrite mediated lipid peroxidation, mitochondrial dysfunction, oligodendrocyte injury, and irreversible axonal damage [1,6,9]. Endogenous antioxidant molecules, including serum uric acid (SUA), have therefore become a topic of scientific interest due to their potential modulatory role in CNS injury.

Uric acid, the final metabolic product of purine degradation in humans, is one of the most potent natural scavengers of peroxynitrite. Experimental models have shown that uric acid reduces

CNS inflammation and protects against peroxynitrite-mediated tissue injury [1,3]. Observational studies have reported lower SUA levels in MS patients compared to

healthy controls [2,4], though not all findings are consistent, indicating that SUA may be influenced by demographic and clinical factors.

Physiological factors such as age and gender significantly determine SUA concentrations, with males typically having higher levels than females due to hormonal influences on renal urate excretion. Since MS primarily affects young adult females, these inherent differences may influence the observed SUA–MS association. Clinical factors including disease duration and disability may also modify SUA levels.

Several studies suggest that lower SUA may correlate with higher disability scores, such as the Expanded Disability Status Scale (EDSS), and may be more pronounced during early or active inflammatory stages of the disease [4,10]. the central nervous system (CNS), characterized by inflammation, myelin loss, axonal degeneration, and progressive neurodegeneration. Oxidative and nitrosative.

The potential impact of diseasemodifying therapies (DMTs) on SUA has gained attention, as some treatments may alter uric acid metabolism indirectly through immune-metabolic pathways, renal function, weight changes, or shifts in purine handling [7,8]. Therefore, controlling for DMT exposure, treatment duration, renal function, BMI, diet, and concomitant medications is essential when evaluating the relationship between SUA and MS.

Given the conflicting findings in the literature and the possibility that SUA reflects both biological processes and treatment-related influences, additional research is necessary to clarify whether SUA acts as a biomarker associated with disease activity, progression, or therapeutic response. This study aims to evaluate the relationship between serum uric acid levels and multiple clinical aspects of MS including age, gender, disease duration, disability, and DMT use—to better understand its potential relevance in MS pathophysiology and clinical management.

2. Materials and methods

2.1 Study design

This case–control study was designed to compare serum uric acid (SUA) levels between patients with MS and age- and sex-matched healthy controls.

Additionally, SUA levels were evaluated in relation to clinical characteristics and disability parameters. The study was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki.

2.2 MS Patient Selection

Patients with MS were recruited from the MS Clinic at Babil Neurology Center in Babil, Iraq. Clinical and laboratory data were recorded during their first scheduled clinical visit in 2024. Trained neurologists evaluated all participants for key MS parameters :

- Disease duration: Years elapsed since reported clinical symptom onset .
- Time from diagnosis: Years elapsed since formal MS diagnosis.
- Disability: Expanded Disability Status Scale (EDSS) score .

- Treatment status: Current diseasemodifying therapy (DMT) and concomitant medications. - Inclusion Criteria:
- Diagnosis of definite MS according to the 2017 McDonald criteria. - Exclusion Criteria:
- Presence of an acute clinical relapse.
- Recent modification of DMT regimen (< 6 months).
- Recent corticosteroid therapy (< 1 month) .
- Treatment with diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), or other urate-modifying medications.
- Co-existing metabolic conditions affecting urate handling (e.g., gout).
- Abnormal body mass index (BMI).

2.3 Control group

Healthy control subjects were recruited from the Internal Medicine Unit of the same hospital during the same enrollment period. All controls underwent routine clinical evaluations. Factors capable of influencing SUA levels— including medical comorbidities, concomitant drug therapy, alcohol consumption, and BMI—were recorded. The exclusion criteria applied to controls were identical to those applied to the MS group.

2.4 Laboratory findings

Venous blood samples were collected under fasting conditions. SUA concentrations were determined using the UA2 enzymatic assay with an ACN700 reagent kit on a COBAS® c501 automated analyzer (Roche Diagnostics). Normal reference ranges for SUA in this laboratory are 142.7–356.9 μmol/L for females and 202.2–416.4 μmol/L for males.

2.5 Statistical analyses

Propensity Score Matching (PSM) with a 1:1 ratio was utilized to match MS patients with controls based on age and sex. Categorical demographic variables were analyzed using the Chi-square (χ^2) test, and continuous variables were compared using Student's t-test. Analysis of Variance (ANOVA) was used to compare SUA levels between MS patients and controls, with secondary adjustment for age, sex, and renal function. Statistical analyses were executed using SPSS and Microsoft Excel. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Demographic Comparison

A total of 44 MS patients and 44 matched healthy controls were included. There were no statistically significant differences between the MS and control groups regarding age (30.4 ± 9.5 years vs. 29.5 ± 9.8 years, $p = 0.69$) or sex distribution (77.3% female vs. 63.6% female, $p = 0.18$), confirming effective matching.

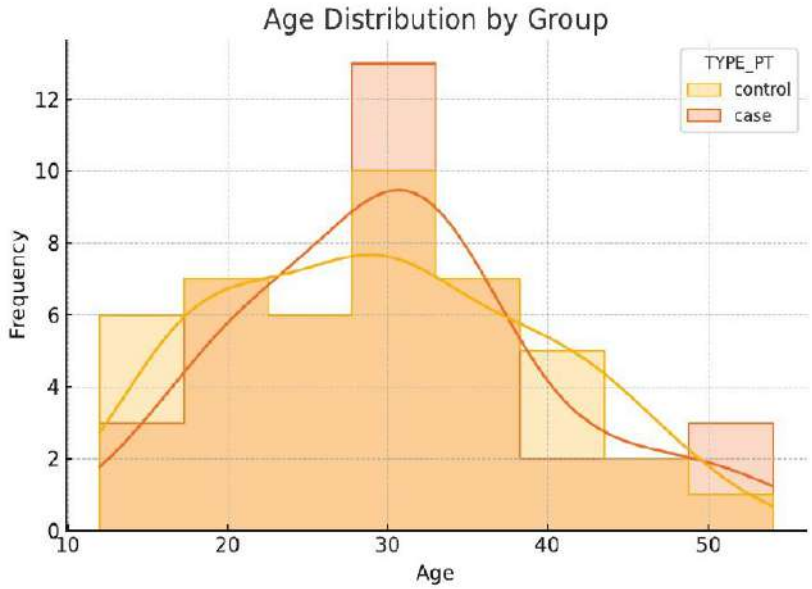

Figure 1: Age distribution by group

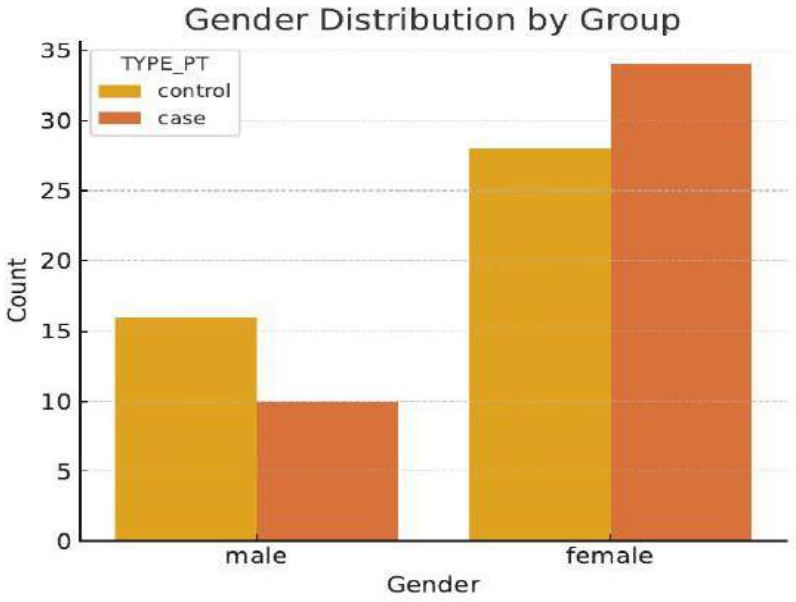

Figure 2: Gender Distribution by group

3.2 Uric Acid Level Comparison

Serum uric acid levels were significantly lower in MS patients than in control subjects (225 ± 79.3 μmol/L vs. 249 ± 77.1 μmol/L, $p = 0.044$). Categorical analysis of SUA (low vs. normal relative to laboratory reference values) revealed a significantly higher proportion of low SUA levels among MS patients (χ^2 test, $p < 0.05$).

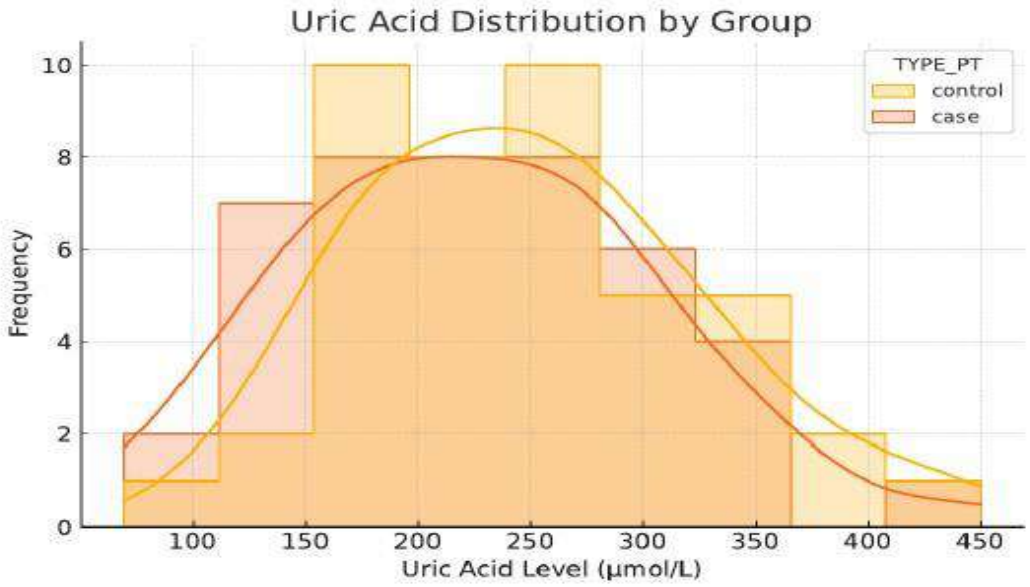

Figure 3: Uric acid distribution by group

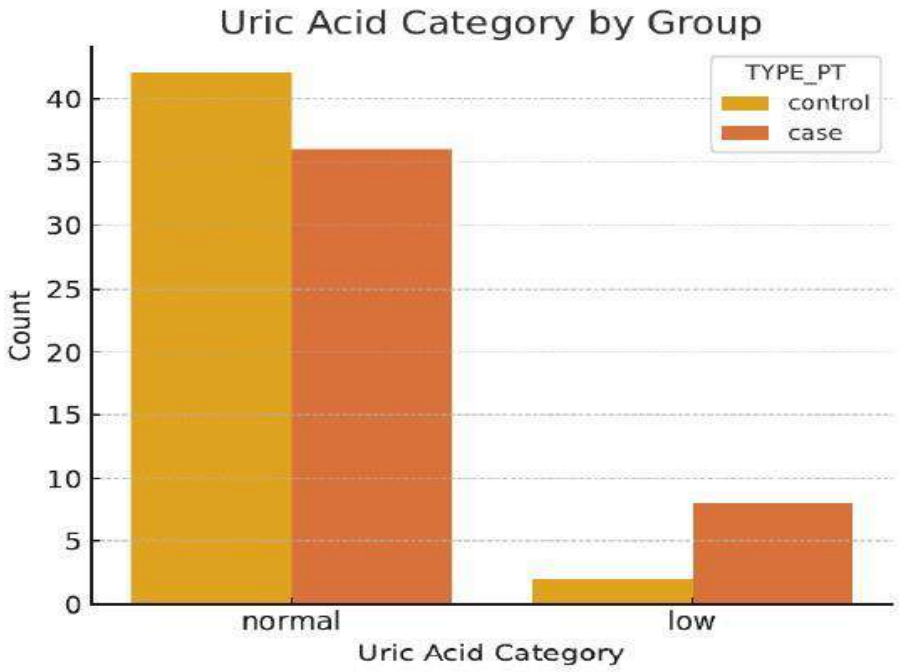

Figure 4: Uric acid category by group

3.3 Association with Clinical Features

Within the MS cohort, SUA levels were evaluated across clinical variables:

- Disability (EDSS): Correlation analysis revealed a weak, non-significant negative association between SUA levels and EDSS score ($r = -0.12$, $p = 0.45$) .
- Disease Duration: SUA concentrations were not significantly associated with disease duration ($p > 0.05$).

- Ambulation Status: No significant difference in SUA levels was observed between fully ambulatory patients (n = 40) and those with impaired ambulation (n = 4) (r = 0.024, p = 0.80).

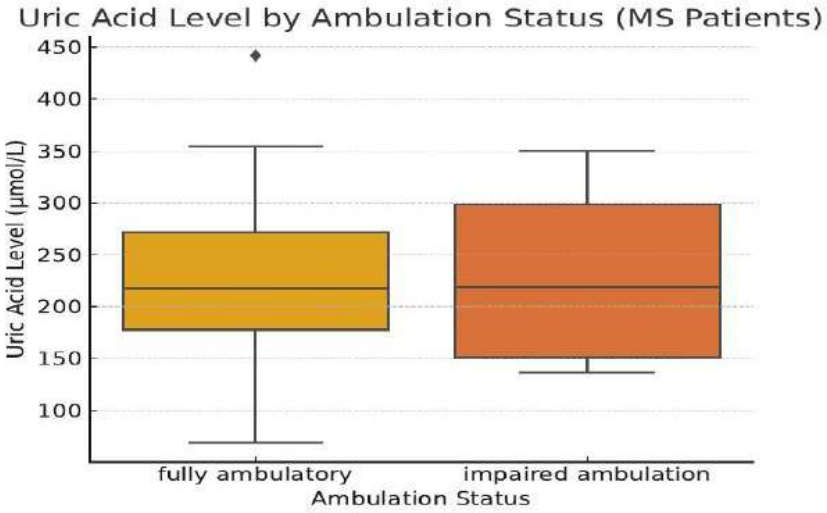

Table1: Demographics and clinical features of subjects with MS and controls

Table 1: Demographics and clinical features of subjects with MS and controls

Parameter	MS Subjects (n = 44)	Controls (n = 44)	p-value
Sex (Male / Female), n (%)	10 / 34 (22.7% / 77.3%)	16 / 28 (36.4% / 63.6%)	0.18
Age (years), Mean ± SD (Range)	30.4 ± 9.5 (12–54)	29.5 ± 9.8 (14–50)	0.69
Serum Uric Acid (µmol/L), Mean ± SD	225 ± 79.3 (69–442)	249 ± 77.1 (100–450)	0.044
Disease Duration (months), Mean ± SD	35 ± 12 (1–204)	N/A	—
EDSS Score, Mean ± SD	1.26 ± 1.7 (0–7.5)	N/A	—
Ambulation (Fully / Impaired), n	40 / 4	N/A	—

3.4 Influence of Disease-Modifying Therapies (DMTs)

ANOVA demonstrated overall variation in SUA levels across different DMT classes ($p < 0.05$). However, Tukey post-hoc pairwise testing revealed no statistically significant differences between specific individual agents. Patients on agents such as Rebif®, Natalizumab, and Rituximab generally maintained normal SUA levels, whereas lower levels were observed in patients treated with Teriflunomide.

Table 2: Influence of Disease-Modifying Therapies (DMTs)

Disease-Modifying Therapy	Low SUA (n)	Normal SUA (n)	Total (n)
Interferon beta-1b (Betaferon®)	1	9	10
Interferon beta-1a (Avonex®)	1	3	4
Interferon beta-1a (Rebif®)	0	7	7
Interferon beta-1a (CinnoVex®)	1	1	2
Interferon beta-1a (Recigen®)	0	1	1
Fingolimod (Gilenya®)	1	2	3
Natalizumab (Tysabri®)	1	10	11
Rituximab	0	3	3
Teriflunomide (Aubagio®)	2	0	2
Ocrelizumab (Ocrevus®)	1	0	1
Total	8	36	44

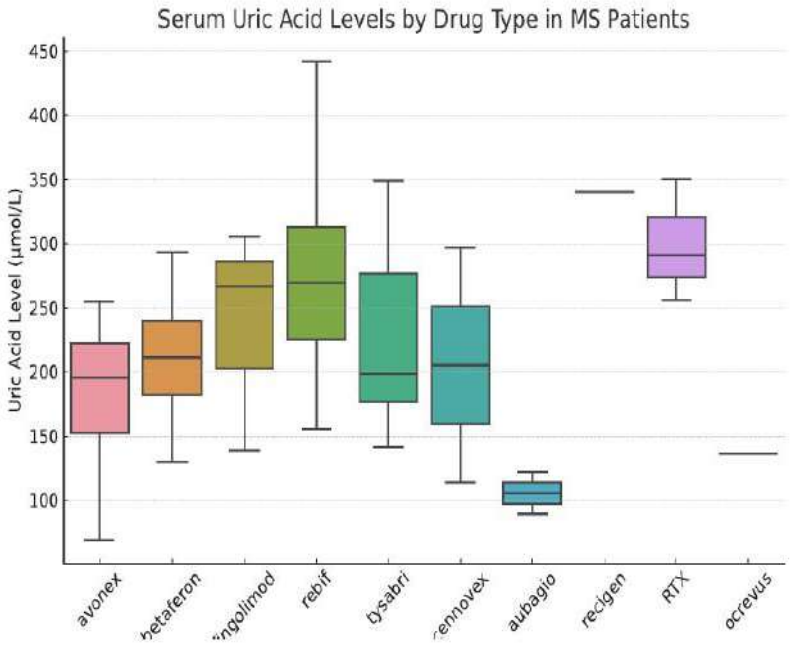

Figure 6: SUA level by drug types in MS patients

4. Discussion

This cross-sectional study evaluated SUA levels in patients with MS relative to healthy controls and explored its correlation with clinical characteristics. Our primary findings demonstrate that MS patients have significantly lower SUA levels compared to healthy controls, aligning with findings from multiple prior studies[4,12,13,14]. These results lend further support to the hypothesis that reduced antioxidant capacity, specifically via diminished uric acid levels, is involved in MS pathophysiology.

In our cohort, gender was not a significant determinant of SUA differences between cases and controls. While this finding is consistent with select reports [16], it contrasts with larger studies

that identified female sex as a predominant driver of lower SUA in MS. This discrepancy is likely attributable to our smaller sample size [4,14,15]. Furthermore, disease duration did not independently correlate with SUA levels, indicating that lower SUA is not simply a cumulative consequence of long-standing disease [4,12,15]. Although patients in acute clinical relapses were excluded, literature indicates that SUA levels fluctuate significantly during active inflammatory relapses.

Regarding treatment, MS patients on DMTs displayed higher mean SUA levels relative to untreated controls in some literature [16,17,18,19], suggesting that immunomodulatory therapies may partially restore endogenous antioxidant status. However, while DMT type significantly influenced SUA categories overall, our post-hoc analysis found no single DMT agent superior to others.

Study Limitations

1) Sample Size: The sample size (n = 44 per arm) limits statistical power for subgroup analyses among specific DMT regimens.
2) Exclusion of Relapsing Patients: Patients experiencing acute relapses were excluded; assessing SUA during acute exacerbations would provide valuable mechanistic insights.
3) Absence of Neuroimaging Data: Magnetic resonance imaging (MRI) 3. Absence of Neuroimaging Data: Magnetic resonance imaging (MRI) metrics were not integrated, preventing evaluation of subclinical radiological activity.

5. Conclusion

Our study confirms that serum uric acid levels are significantly reduced in patients with MS compared to age- and sexmatched healthy controls. While SUA levels varied across DMT treatment groups, they did not correlate with physical disability (EDSS), disease duration, or ambulation status. These findings support SUA as a potential diagnostic biomarker and secondary indicator of treatment response in MS.

Recommendations

- Longitudinal prospective studies with larger cohort sizes to evaluate SUA variations across specific DMTs.
- Comparative measurements of SUA during clinical relapse versus remission phases.
- Inclusion of advanced neuroimaging parameters to correlate SUA with subclinical inflammatory activity and brain atrophy metrics.

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