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Study of Serum Lactate Dehydrogenase Levels in Patients of Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) patients face a 1.5-fold higher cardiovascular risk, with elevated homocysteine—driven by nutritional deficiencies, medications, and malabsorption—promoting endothelial dysfunction, oxidative stress, and NF-κB-mediated inflammation that worsens both vascular and joint damage. This cross-sectional study assessed serum homocysteine and lactate dehydrogenase (LDH) levels as potential biomarkers of disease activity in 127 diagnosed RA patients (≥18 years) at Gandhi Medical College/Hamidia Hospital, Bhopal. Homocysteine was measured by competitive inhibition ELISA (MicroLab Reader) and LDH by the LDH (L-P) IFCC method on a Beckman Coulter AU5800 Analyzer. Serum homocysteine was highest in patients with disease duration <8 weeks (40 patients, 71%) and declined significantly with longer duration (8–16 weeks: 2.2%; >16 weeks: 0%; p <0.001), with notably higher levels observed in small joint involvement compared to large joint involvement. All 127 patients had LDH activity above the normal range, with 96.4% of those in the <8-week disease duration group showing markedly elevated LDH (421–560 U/L and >560 U/L). These findings indicate that approximately one-third of RA patients exhibit elevated homocysteine—particularly among younger individuals—and that the early co-elevation of both homocysteine and LDH reflects active autoimmune-driven metabolic dysregulation, supporting their role as reliable biomarkers of disease activity and underscoring the importance of early therapeutic intervention to mitigate long-term cardiovascular and articular complications.

Keywords*: Rheumatoid arthritis, Homocysteine, Lactate dehydrogenase (LDH), Autoimmunity, Biomarkers.*

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease primarily affecting synovial joints, characterized by persistent inflammation, progressive joint destruction, and systemic manifestations that can lead to irreversible deformity and functional disability if inadequately managed. Its pathophysiology involves genetic predisposition, environmental triggers, and immune dysregulation, culminating in synovial hyperplasia, pannus formation, and cartilage and bone erosion (Scherer et al., 2020). RA is a significant global health concern, affecting 0.5–1% of the world's population (Almutairi et al., 2021; Shi et al., 2025), and approximately 0.28–0.75% of the adult Indian population (Malaviya et al., 1993).

Lactate dehydrogenase (LDH), a ubiquitous cytoplasmic enzyme catalyzing the reversible conversion of lactate to pyruvate, has gained attention as a biomarker of RA disease activity, with elevated levels reflecting increased cellular turnover, tissue damage, and metabolic demands of chronic inflammation (Patel et al., 2018). The interplay between these

biomarkers underscores the multifaceted nature of RA, offering valuable insights into disease pathophysiology, activity assessment, and treatment monitoring, thereby supporting improved diagnostic and therapeutic strategies.

Despite growing evidence supporting the role of homocysteine and LDH in RA pathophysiology, their combined utility as disease activity markers—particularly in relation to disease duration, joint involvement pattern, and treatment status—remains underexplored in the Indian population. The present study was therefore undertaken to evaluate serum homocysteine and LDH levels in RA patients at a tertiary care centre and assess their association with clinico-demographic variables.

MATERIALS AND METHODS

This was an observational cross-sectional study conducted at the Department of Biochemistry in collaboration with the Department of Medicine, Gandhi Medical College and Hamidia Hospital, Bhopal, over a duration of 18 months. The study included 127 subjects of either sex, diagnosed with Rheumatoid Arthritis within the previous 5 years as per the 2010 ACR/EULAR criteria (Aletaha et al., 2010; Kay & Upchurch, 2012), aged 18 years or above, attending the Medicine OPD. Patients with any other autoimmune disease, other types of arthritis, conditions requiring frequent blood transfusions, or those who were pregnant or lactating were excluded.

The sample size was calculated using the formula $n = z^2p(1-p)/d^2$, with a 95% confidence level ($z = 1.96$) and 5% precision. Ethical clearance was obtained from the Institutional Ethics Committee of Gandhi Medical College, and written informed consent was obtained from all participants in their preferred language.

Blood specimens were collected by venepuncture from the antecubital vein, allowed to clot, and serum was separated by centrifugation at 3000 rpm for 15 minutes. All biochemical analyses were performed in the Biochemistry laboratory following NCCLS standards. Serum Lactate Dehydrogenase (LDH) was estimated by the IFCC-recommended kinetic UV method using a Beckman Coulter AU5800 Series analyzer. The method is based on LDH-catalyzed conversion of L-lactate to pyruvate with simultaneous reduction of NAD^+ to NADH, measured spectrophotometrically at 340 nm; normal reference range: 140–280 U/L. Rheumatoid Factor (RF) was quantified by latex-enhanced immunoturbidimetry on the Beckman Coulter AU5800 analyzer; values ≤14 IU/mL are considered normal.

RESULTS

A total of 127 RA patients were enrolled. The majority were female (60.6%; F:M ratio ~1.5:1), and the predominant age group was 41–60 years (52.8%). Regarding disease duration, 44.1% had early RA (<8 weeks), 36.2% had intermediate duration (8–16 weeks), and 19.7% had longer duration (>16 weeks). Small joint involvement was predominant (87.4%), and most patients (83.5%) were on methotrexate therapy (Table 1).

All 127 patients had serum LDH levels above the normal range (140–280 U/L), with a mean of 447.80 ± 93.71 U/L. The majority (34.6%) showed levels 50–100% above normal (Table 2). Males had significantly higher mean LDH than females (470.40 ± 85.31 vs. 433.12 ± 96.49 U/L; $p = 0.028$) (Table 4), though categorical distribution by gender was not significant ($p = 0.062$). Age group differences in LDH were not statistically significant (ANOVA $p = 0.250$) (Table 3).

Disease duration showed a strong inverse relationship with LDH activity: patients with <8 weeks duration had the highest mean LDH (532.32 ± 67.42 U/L), followed by the 8–16 weeks group (390.43 ± 45.94 U/L) and the >16 weeks group (364.00 ± 37.86 U/L), with highly significant differences ($F = 118.806$; $p < 0.001$) (Table 5). Small joint involvement was associated with significantly higher LDH (462.79 ± 89.69 U/L) compared to large joint involvement (343.75 ± 39.48 U/L; $p < 0.001$) (Table 6). Patients not on methotrexate had higher mean LDH (485.71 ± 71.38 U/L) than those on treatment (440.28 ± 96.03 U/L; $p = 0.042$) (Table 7).

Table 1. Demographic and clinical profile (n = 127)

Variable	Category	n	(%)
Age group (years)	≤20	5	3.9
	21–30	—	—
	31–40	23	18.1
	41–50	35	27.6
	51–60	32	25.2
	>60	20	15.7
Gender	Female	77	60.6

Variable	Category	n	(%)
	Male	50	39.4
Disease duration	<8 weeks	56	44.1
	8–16 weeks	46	36.2
	>16 weeks	25	19.7
Joint involvement	Small joints	111	87.4
	Large joints	16	12.6
Methotrexate use	Yes	106	83.5
	No	21	16.5

Table 2. Serum LDH elevation categories (n = 127)

LDH range (U/L)	Elevation above normal	n	%
280–350	<25% above normal	22	17.3
351–420	25–50% above normal	41	32.3
421–560	50–100% above normal	44	34.6
>560	>100% above normal	20	15.7

Normal range: 140–280 U/L. All 127 patients had LDH above normal. Overall mean ± SD: 447.80 ± 93.71 U/L.

Table 3. Mean serum LDH by age group (ANOVA)

Age group (Years)	Mean LDH (U/L)	SD
≤20	394.00	75.03
21–30	498.33	78.95
31–40	~432	—
41–50	~463	—
51–60	~450	108.35
>60	~440	—
Overall	447.80	93.71

F = 1.346; p = 0.250 (not significant)

Table 4. Mean serum LDH by gender (t-test)

Gender	n	Mean LDH (U/L)	SD	t	p-value
Male	50	470.40	85.31	−2.225	0.028*
Female	77	433.12	96.49		

*Statistically significant (p < 0.05)

Table 5. Mean serum LDH by disease duration (ANOVA)

Disease duration	n	Mean LDH (U/L)	SD	F	p-value
<8 weeks	56	532.32	67.42	118.806	<0.001*
8–16 weeks	46	390.43	45.94		
>16 weeks	25	364.00	37.86		

*Statistically significant (p < 0.05). LDH decreases as disease duration increases.

Table 6. Mean serum LDH by joint involvement (t-test)

Joint type	n	Mean LDH (U/L)	SD	t	p-value
Small joints	111	462.79	89.69	−5.223	<0.001*
Large joints	16	343.75	39.48		

*Statistically significant ($p < 0.05$)

Table 7. Mean serum LDH by methotrexate use (t-test)

Methotrexate	n	Mean LDH (U/L)	SD	t	p-value
No	21	485.71	71.38	−5.148	0.042*
Yes	106	440.28	96.03		

*Statistically significant ($p < 0.05$). Categorical chi-square: $p = 0.074$ (not significant).

DISCUSSION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease primarily affecting synovial joints, leading to progressive joint destruction, disability, and premature mortality if untreated. As a multisystem disorder, RA also involves cardiovascular, pulmonary, and ocular systems (Chauhan et al., 2023; Smolen et al., 2018). This study evaluated serum levels of lactate dehydrogenase (LDH) and homocysteine as biochemical biomarkers in RA patients, examining their clinical significance in relation to disease activity, demographic variables, disease duration, joint involvement pattern, and methotrexate (MTX) usage.

4.1 Age and Gender Distribution

Among 127 enrolled RA patients, the majority (70.9%) were middle-aged (31–60 years), with the largest group in the 41–50 years range (27.6%). This is consistent with Indian epidemiological studies (Misra et al., 2024), though contrasting with global data reporting peak incidence at 65–69 years (Black et al., 2023). The discrepancy likely reflects India's younger demographic profile, earlier disease onset due to genetic and environmental factors, and tertiary care referral patterns.

Female patients predominated (60.6%; F:M ratio ≈1.5:1), consistent with RA's well-established female predisposition (global F:M ratio 2.45:1) (Black et al., 2023). The moderately lower ratio observed may reflect regional genetic influences, differential healthcare-seeking behaviour, or hormonal variation. Female predominance and middle-aged peak are attributed to autoimmune mechanisms, estrogen fluctuations during perimenopause/menopause affecting immune regulation, and MTHFR C677T polymorphism influencing inflammatory pathways (Chaabane et al., 2018; Chauhan et al., 2023).

4.2 Disease Duration and Joint Involvement

Most patients had early RA (<8 weeks: 44.1%; 8–16 weeks: 36.2%), with 80.3% having disease duration ≤16 weeks. Small joint involvement was predominant (87.4%), reflecting the classic symmetric polyarthritis of RA involving MCP, PIP, and MTP joints (Malaviya et al., 1993). These findings reflect the impact of the 2010 ACR/EULAR classification criteria (Aletaha et al., 2010), which emphasise early disease features, enabling timely intervention within the critical therapeutic window to prevent irreversible joint damage.

4.3 Methotrexate Usage

Methotrexate was being used by 83.5% of patients, consistent with current evidence-based guidelines positioning MTX as the anchor conventional synthetic DMARD in RA management owing to its favourable efficacy, safety, and cost-effectiveness (Smolen et al., 2023). This high adoption rate confirms appropriate standard-of-care implementation in the present cohort.

4.4 Serum Lactate Dehydrogenase (LDH) Activity

All 127 RA patients had elevated serum LDH above the normal reference range (140–280 U/L), with a mean of 447.80 ± 93.71 U/L. Yang et al. (2024) identified key genes in LDH-related lactate metabolism regulating macrophage function in RA. Souto-Carneiro et al. (2020) demonstrated 2.6–3.7-fold higher lactate production in RA CD8+ T cells, with overexpression of LDHA across all subsets. These findings indicate metabolic reprogramming toward aerobic glycolysis (Warburg effect) as a driver of systemic LDH elevation in RA (Gupta, 2022). Conversely, Patel et al. (2018) found no proportional rise in serum LDH relative to disease severity (CDAI and DAS28-CRP), suggesting limitations of total serum LDH as a standalone severity marker.

The pathophysiological basis includes: (i) metabolic reprogramming of immune cells (synovial fibroblasts, T cells, B cells, macrophages) toward aerobic glycolysis with increased lactate and LDH release; (ii) pro-inflammatory cytokines (TNF-α, IL-1β) increasing cellular membrane permeability promoting LDH leakage; and (iii) chronic synovial inflammation

perpetuating cellular activation, proliferation, and apoptosis with ongoing LDH release (Souto-Carneiro et al., 2020; Gupta, 2022).

4.5 Age and Gender Variations in LDH

Mean serum LDH was highest in the 21–30 age group (498.33 ± 78.95 U/L), possibly reflecting more aggressive early-onset disease, and lowest in the ≤20 age group (394.00 ± 75.03 U/L). However, ANOVA showed no statistically significant difference across age groups ($F = 1.346$, $p = 0.250$), indicating LDH elevation is a consistent feature of RA irrespective of age. Males had significantly higher mean LDH (470.40 ± 85.31 U/L) compared to females (433.12 ± 96.49 U/L) ($t = -2.225$, $p = 0.028$). This may be attributed to higher baseline muscle mass and differing muscle fibre composition in males, alongside gender-specific hormonal influences on inflammatory cell activation (Gupta, 2022).

STRENGTHS AND LIMITATIONS

The universal elevation of serum LDH across all 127 patients, with statistically significant associations with gender ($p = 0.028$), disease duration ($p < 0.001$), joint involvement ($p < 0.001$), and methotrexate usage ($p = 0.042$), supports its utility as a consistent inflammatory marker in RA. However, LDH lacks diagnostic specificity, being elevated in hemolysis, hepatic disease, malignancy, and myocardial injury. LDH isoenzyme profiling was not performed, limiting mechanistic interpretation. LDH levels were not correlated with validated disease activity scores such as DAS28 or CDAI, and the cross-sectional design precludes causal inference.

CONCLUSION

Serum lactate dehydrogenase (LDH) emerged as a consistently elevated and clinically significant biomarker in patients with rheumatoid arthritis, reflecting the underlying metabolic and inflammatory burden of the disease. The highest LDH levels were observed in patients with early-stage disease, small joint involvement, and those not receiving adequate disease-modifying therapy, indicating a strong association between LDH elevation and active inflammatory processes. The significantly greater elevation noted in male patients further suggests the influence of biological and hormonal factors on inflammatory cellular injury.

These findings support the incorporation of serum LDH into routine biochemical assessment as a simple, responsive, and cost-effective indicator for evaluating disease activity, monitoring therapeutic response, and identifying patients with high inflammatory burden, particularly during the early and clinically active stages of rheumatoid arthritis. Future studies should incorporate LDH isoenzyme profiling, correlation with validated disease activity scores, and longitudinal follow-up to further delineate its prognostic utility.

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REFERENCES

1. Aletaha, D., Neogi, T., Silman, A. J., Funovits, J., Felson, D. T., Bingham, C. O., et al. (2010). 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & Rheumatism, 62(9), 2569–2581. https://doi.org/10.1002/art.27584
2. Almutairi, K., Nossent, J., Preen, D., Keen, H., & Inderjeeth, C. (2021). The global prevalence of rheumatoid arthritis: A meta-analysis based on a systematic review. Rheumatology International, 41(5), 863–877. https://doi.org/10.1007/s00296-020-04731-0
3. Black, R. J., Cross, M., Haile, L. M., Culbreth, G. T., Steinmetz, J. D., Hagins, H., et al. (2023). Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: A systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology, 5(10), e594–e610. https://doi.org/10.1016/S2665-9913(23)00211-4
4. Chaabane, S., Messedi, M., Akrout, R., Ben Hamad, M., Turki, M., Marzouk, S., et al. (2018). Association of hyperhomocysteinemia with genetic variants in key enzymes of homocysteine metabolism and methotrexate toxicity in rheumatoid arthritis patients. Inflammation Research, 67(8), 703–710. https://doi.org/10.1007/s00011-018-1161-8
5. Chauhan, K., Jandu, J. S., Brent, L. H., & Al-Dhahir, M. A. (2023). Rheumatoid arthritis. In StatPearls [Internet]. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK441999/
6. Gupta, G. S. (2022). The lactate and the lactate dehydrogenase in inflammatory diseases and major risk factors in COVID-19 patients. Inflammation, 45(6), 2091–2123. https://doi.org/10.1007/s10753-022-01680-7
7. Kay, J., & Upchurch, K. S. (2012). ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology, 51(Suppl 6), vi5–vi9. https://doi.org/10.1093/rheumatology/kes279

8. Malaviya, A. N., Kapoor, S. K., Singh, R. R., Kumar, A., & Pande, I. (1993). Prevalence of rheumatoid arthritis in the adult Indian population. Rheumatology International, 13(4), 131–134. https://doi.org/10.1007/BF00301258
9. Misra, D. P., Sharma, A., Dharmanand, B. G., & Chandrashekara, S. (2024). The epidemiology of rheumatic diseases in India. Indian Journal of Rheumatology, 19(1), 54–61. https://doi.org/10.1177/09733698241229779
10. Patel, D., Patel, M., Patel, A., Patel, G., Patel, V., & Patel, M. (2018). Can serum lactate dehydrogenase be used as a disease severity biochemical marker in rheumatoid arthritis? IOSR Journal of Dental and Medical Sciences, 17, 01–03. https://doi.org/10.9790/0853-1710010103
11. Scherer, H. U., Häupl, T., & Burmester, G. R. (2020). The etiology of rheumatoid arthritis. Journal of Autoimmunity, 110, 102400. https://doi.org/10.1016/j.jaut.2019.102400
12. Shi, W., Liang, X., Zhang, H., & Li, H. (2025). Burden of rheumatoid arthritis in India from 1990 to 2021: Insights from the Global Burden of Disease Database. Frontiers in Medicine, 12. https://doi.org/10.3389/fmed.2025.1526218
13. Smolen, J. S., Aletaha, D., Barton, A., Burmester, G. R., Emery, P., Firestein, G. S., et al. (2018). Rheumatoid arthritis. Nature Reviews Disease Primers, 4(1), 18001. https://doi.org/10.1038/nrdp.2018.1
14. Smolen, J. S., Landewé, R. B. M., Bergstra, S. A., Kerschbaumer, A., Sepriano, A., Aletaha, D., et al. (2023). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Annals of the Rheumatic Diseases, 82(1), 3–18. https://doi.org/10.1136/ard-2022-223356
15. Souto-Carneiro, M. M., Klika, K. D., Abreu, M. T., Meyer, A. P., Saffrich, R., Sandhoff, R., et al. (2020). Effect of increased lactate dehydrogenase A activity and aerobic glycolysis on the proinflammatory profile of autoimmune CD8+ T cells in rheumatoid arthritis. Arthritis & Rheumatology, 72(12), 2050–2064. https://doi.org/10.1002/art.41420
16. Yang, F., Shen, J., Zhao, Z., Shang, W., & Cai, H. (2024). Unveiling the link between lactate metabolism and rheumatoid arthritis through integration of bioinformatics and machine learning. Scientific Reports, 14(1), 9166. https://doi.org/10.1038/s41598-024-59907-6