

Significance of Elevated Synovial Fluid Lactic Acid and Lactate Dehydrogenase Levels in Differentiating Between Septic Arthritis, Inflammatory Arthritis and Non-Inflammatory Arthritis

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ABSTRACT

Objective: To determine the lactic acid and lactate dehydrogenase levels in synovial fluid and differentiate between inflammatory and non-inflammatory arthritis.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Rheumatology, Liaquat National Hospital, Karachi, from Feb to May 2019.

Methodology: All patients of age >18 years, of either gender, who presented with knee joint effusion were enrolled in the study. Synovial fluid aspiration for the analysis of lactate and lactate dehydrogenase (LDH) was done for all patients.

Results: Seventy-seven patients were enrolled, of which 75 were included in the analysis. Two patients were excluded as one had lymphoma and the other had recent joint trauma. 31 (41.3 %) patients had non-inflammatory, or osteoarthritis, and 44 (58.7 %) had inflammatory arthritis. The mean value of synovial LDH in inflammatory and non-inflammatory arthritis was 737.38 ± 102.76 mmol/L and 265.5 ± 17.43 mmol/L, respectively, ($p < 0.001$). The mean value of synovial lactate in inflammatory arthritis (32.16 ± 2.84 mmol/L) was higher than the mean value of synovial lactate in non-inflammatory arthritis (19.81 ± 1.08 mmol/L) ($p < 0.001$). There mean plasma LDH in inflammatory arthritis and non-inflammatory arthritis was 495.77 ± 41.67 mg/dl and 437.90 ± 30.99 mg/dl, respectively ($p > 0.05$). The plasma lactate in inflammatory arthritis and non-inflammatory arthritis was 12.84 ± 0.59 mg/dl and 12.97 ± 0.78 mg/dl, respectively ($p > 0.05$).

Conclusion: Synovial fluid lactic acid and synovial LDH can serve as rapid diagnostic and cost-effective tests to differentiate between non-inflammatory and inflammatory arthritis.

Keywords: Arthritis, Lactate dehydrogenase, Synovial fluid.

How to Cite This Article: Erum U, Umer TP, Arain SUR, Ahmed MR, Nazir L. Significance of Elevated Synovial Fluid Lactic Acid and Lactate Dehydrogenase Levels in Differentiating Between Septic Arthritis, Inflammatory Arthritis and Non-Inflammatory Arthritis. *Pak Armed Forces Med J* 2022; 72(Suppl-2): S276-279. DOI: <https://10.51253/pafmj.v72iSUPPL-2.3996>

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INTRODUCTION

The synovial fluid analysis is considered an imperative tool in the diagnosis and treatment of various types of arthritis.¹ However, certain studies suggest lactic acid (LA) or lactate dehydrogenase (LDH) assessment in synovial fluid as an exceptional diagnostic test to differentiate between inflammatory and non-inflammatory arthritis. In addition, it may help to discriminate between native and peri-prosthetic joint infections.² One study reported that synovial lactate >10 mmol/L is certainly suggestive of septic arthritis.³

Moreover, an increased concentration of LA has been reported in the synovial fluid of Rheumatoid arthritis (RA) patients, and it may serve as a biomarker for disease progression in RA patients.⁴ In another study, an increased level of synovial d-lactate had shown high sensitivity for prosthetic joint infections.⁵ Thus, synovial LDH is considered a reliable indicator for differentiating inflammatory versus

noninflammatory arthritis.⁶ Furthermore, high lactate level has also been reported in synovial fluid of seropositive RA patients as compared to seronegative RA patients, which indicates that high disease activity state leads to high inflammatory exudate, hence raised lactate and LDH.^{7,8}

Lactate and LDH levels in synovial fluid can serve as a potential biomarker to differentiate between septic and other types of arthritis. However, their significance is evaluated only in septic arthritis and somewhat in inflammatory arthritis. Early and prompt treatment in arthritis, especially in septic and inflammatory arthritis, significantly decreases morbidity and mortality. Pathogenic mechanism suggests that increased synovial LDH and lactate accrue due to increased cell disruption within the synovial fluid secreted by inflamed synovium. Hence, identifying these metabolic alterations may provide insights into the disease mechanisms operating in patients with inflammatory arthritis. Therefore, this study was designed to ascertain if lactate and LDH levels could serve as a rapid marker to differentiate between inflammatory versus the non-inflammatory type of arthritis.

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Received: 01 Jun 2020; revision received: 05 Aug 2020; accepted: 10 Aug 2020

METHODOLOGY

This cross-sectional study was conducted at the Department of Rheumatology, Liaquat National Hospital, Karachi, from February 2019 to May 2019, after approval from the Institutional Ethical Review Board. Informed consent was taken from all the patients. The sample size was 77 patients, which was calculated by using the formula $(n = z^2 \times p(1-p) / \alpha^2)$ by taking the prevalence of lactate in patients with septic arthritis at 5.3%, the margin of error (d) at 5% and the confidence level at 95%.⁹

Inclusion Criteria: All the adult patients of age >18 years, of either gender, who presented with unilateral or bilateral knee joint effusion were enrolled in the study.

Exclusion Criteria: Patients with primary or secondary bone tumours, such as osteosarcoma, multiple myeloma or lymphoma, were excluded. Patients with a history of trauma were also excluded.

Presence of normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (normal ESR <20 mm/1hour, normal CRP <0.1 mg/L) and synovial fluid cell count <2000 cells/cmm were labelled as non-inflammatory arthritis.¹⁰ The presence of high ESR or high CRP and synovial fluid cell count of 2000-20000 cells/cm were labelled as inflammatory arthritis. Presence of high ESR or high CRP and synovial fluid cell count >50000 cells/cmm or positive synovial fluid culture were labelled as inflammatory arthritis.¹¹

A detailed history and examination were taken from all the study participants. All the patients underwent diagnostic joint fluid aspiration. About 2-3ml of synovial fluid was collected using aseptic joint aspiration. Aspirated joint fluid was sent for laboratory analysis, where centrifugation without anticoagulation was done. The analysis of lactate and LDH was deter-

mined on the supernatant fluid within 2 hours, using L-Lactate PAP enzymatic colorimetric and DGKC methods, respectively. In suspected cases of gout, synovial fluid was also examined for the polarized microscope monosodium urate crystals (MSU). Venous blood samples for CBC, creatinine, ESR, CRP, serum

lactic acid and serum LDH levels were also measured. All the demographic features, type of inflammatory arthritis, disease duration, and laboratory results were recorded in a pre-designed proforma. Statistical Package for Social Sciences (SPSS) version 21.0 was used for the data analysis. Frequencies and percentages were computed for qualitative variables like gender and type of arthritis. Quantitative variables were presented as mean \pm standard deviation (SD). An independent sample t-test was applied to determine the significance of inflammatory versus non-inflammatory arthritis. The *p*-value of ≤ 0.05 was considered for the level of significance.

RESULTS

A total of 77 patients were enrolled in the study, of which two patients were excluded as one of them had lymphoma and the other had recent joint trauma. A total of 75 patients were included in the final analysis. The mean age of the patients was 51.43 ± 12.19 years. Among all, 31 (41.3%) patients had non-inflammatory (osteoarthritis/OA/NIF), 44 (58.7%) had inflammatory arthritis. The mean value of synovial LDH (SLDH) in inflammatory arthritis (IA) (737.38 ± 102.76 mmol/L) was significantly higher ($p < 0.001$) than the mean value of SLDH in non-inflammatory arthritis (NIA) (265.5 ± 17.43 mmol/L). The mean value of synovial lactate (SLACT) in inflammatory arthritis (32.16 ± 2.84 mmol/L) was also significantly higher ($p < 0.001$) than the mean value of SLACT in non-inflammatory arthritis (19.81 ± 1.08 mmol/L). The mean plasma LDH (PLDH) in inflammatory arthritis and non-inflammatory arthritis was 495.77 ± 41.67 mg/dl and 437.90 ± 30.99 mg/dl, respectively ($p > 0.05$). The plasma lactate (PLACT) in IA (12.84 ± 0.59 mg/dl) was almost comparable to PLACT of NIA (12.97 ± 0.78 mg/dl), ($p > 0.05$) (Table).

Table: Lab values of inflammatory and non-inflammatory arthritis.

	Inflammatory arthritis (n=44)	Non-inflammatory arthritis (n=31)	<i>p</i> -value
Synovial Lactate dehydrogenase (LDH) (U/L)	737.38 ± 102.76	265.5 ± 17.43	$p < 0.001$
Synovial Lactate (mmol/L)	32.16 ± 2.84	19.81 ± 1.08	$p < 0.001$
Plasma Lactate dehydrogenase (LDH) (U/L)	495.77 ± 41.67	437.90 ± 30.99	$p > 0.05$
Plasma Lactate (mmol/L)	12.84 ± 0.59	12.97 ± 0.78	$p > 0.05$

mined on the supernatant fluid within 2 hours, using L-Lactate PAP enzymatic colorimetric and DGKC methods, respectively. In suspected cases of gout, synovial fluid was also examined for the polarized microscope monosodium urate crystals (MSU). Venous blood samples for CBC, creatinine, ESR, CRP, serum

In inflammatory arthritis, the synovial LDH was significantly higher than the plasma LDH ($p < 0.001$), and synovial lactate was significantly higher than the plasma Lactate ($p < 0.001$). In NIF, the synovial LDH was non-significantly lower than the plasma LDH

($p > 0.05$), but synovial lactate was significantly higher than the plasma lactate ($p > 0.05$).

DISCUSSION

Synovial fluid analysis is a well-established procedure in the evaluation of joint disease. The metabolism of the synovium is determined by many factors, such as intra-articular pressure, obliterative microangiopathy and histologic changes, including hyperplasia of the synovial lining cells and infiltration of inflammatory cells. Infiltration of macrophages is commonly seen in the synovium of both rheumatoid and osteoarthritic patients.¹⁰ Pro-angiogenic factors mediated through various inflammatory cytokines alter the synovial endothelial cell functions hence increasing the disease severity in RA synovium.¹¹ In addition to this, inflammatory changes seen in osteoarthritis could be due to the infiltration of plasma cells and lymphocytes within the synovium.¹²

Synovial fluid aspiration in patients with joint effusion is a routine practice. It has a significant impact on the diagnosis and the management of patients with joint effusions. RA associated fibroblast-like synoviocytes may exhibit an intrinsic glycolytic activity due to an increased influx of pro-inflammatory cytokines.¹³ Moreover, lactate and pyruvate serve as substrates for synovial metabolism in RA, which stimulates abnormal cell proliferation, angiogenesis and pannus formation.¹⁴ Synovial fluid lactate and LDH levels are the specific test of synovial fluid that helps in the rapid diagnosis and differentiation among noninflammatory, inflammatory and infectious arthritis. Our study reported clinically significant lactate and LDH in synovial fluids of patients with inflammatory arthritis and points toward the importance of synovial LDH and lactate assessment in the rapid identification of inflammatory arthritis, especially in patients with diagnostic difficulty. Our findings are comparable to previous studies, which also showed raised serum and synovial fluid LDH levels in patients with RA.^{15,16} In an Indian study, synovial LDH, alkaline phosphatase and anti-citrullinated peptide (ACP) were reported to be higher in RA patients compared to those with osteoarthritis.¹⁷ However, in another Indian study, no relation was established between raised LDH and disease severity of RA, despite the raised level of LDH within synovium.¹⁸ Nonetheless, no correlation with disease activity was determined in our study, as this was beyond the scope of the present study.

It is assumed that a high lactate concentration results from increased glucose utilization and conver-

sion to lactic acid under anaerobic conditions in the inflamed synovium. The presence of lactate and LDH in active synovitis has long been known as obligatory to the metabolism of synovium by bacterial infections resulting in septic arthritis. It has been reported that early diagnosis and immediate therapy are prudent to improve morbidity in patients with septic arthritis.¹⁹ Therefore, it is imperative for emergency physicians to deploy rapid tests such as SLDH and SLACT to optimize clinical diagnosis because even a single dose of antibiotic may cloud the interpretation of synovial fluid bacterial cultures.²⁰ A recent study has also reported the advantage of synovial D-lactate test as it requires low synovial fluid volume, short turn-around time and low cost.²¹ Furthermore, the increased neutrophils during the acute phase of inflammatory joint disorders contribute to the enhanced inflammatory cell recruitment within the synovium.²² Hence, we can postulate that this increased cell turnover in the synovial fluid leads to increased lactate levels both in synovium and plasma of patients with inflammatory joint diseases. Nonetheless, a significant rise in synovial lactate was also seen in many patients with non-inflammatory arthritis (OA) in our study, which is comparable to that reported by Hurter *et al.*²³

Prior studies conducted in Pakistan reported that elevated lactate and LDH levels in the synovial fluid correspond with the positive bacterial culture from synovial fluid hence suggesting its role in early diagnosis of septic arthritis and differentiating it from non-septic causes.^{24,25} None of the patients was diagnosed with septic arthritis during the study period, hence the role of both these rapid test, i.e. SLDH and SLACT could not suggest their diagnostic utility in this regard. Our study shows that patients with inflammatory joint diseases have higher synovial lactate and LDH levels. Both of these tests, being rapid diagnostic tests, can easily be applicable in clinical practice, compared to other modalities such as synovial fluid culture and MRI of the affected joints, in terms of time consumption and cost, especially where prompt and rapid diagnosis is required. In addition, the study results suggest that high synovial fluid lactate and LDH suggest inflammatory arthritis and the low level of synovial lactate points to the exclusion of the diagnosis of inflammatory or infectious arthritis. Synovial fluid lactic acid and synovial LDH can serve as rapid diagnostic and cost-effective tests to differentiate between non-inflammatory and inflammatory arthritis. Moreover, we suggest that further diagnostic trials or longitudinal studies of undiagnosed cases of arthritis

should be undertaken to evaluate the role of the clinical gestalt and the efficacy of non-traditional synovial markers such as synovial lactate and LDH.

CONCLUSION

Synovial fluid lactic acid and synovial LDH can serve as rapid diagnostic and cost-effective tests to differentiate between non-inflammatory and inflammatory arthritis.

Conflict of Interest: None.

Authors' Contribution

UE: Direct contribution, TPUL, SURA,; MRA,; LN: Intellectual contribution.

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