ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Review Article

Synovial Fluid Lactate for the Diagnosis of Joint Infection: A Systematic Review

Adel Hossny Hegaze[1]*, Walied Abdulaziz Alaleet[2], Ahmad Mohammed Alghraibi[3], Abdullah Mohammed Asiri[4], Fahad Saad Alshahrani[4], Abdulrahman Mudhhi Alabdali[5], Taher Ahmed Babkr[5], Mohammed Hamdan Alghamdi[5], Yasser Abdulrhman Alessa[4], Nasser Abdulrhman Altamimi[6] and Faisal Fahad Alshammari[6]

[1]*Assitant Professor, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia*

[2]*Department of Orthopaedics, Buraydah Central Hospital, Buraydah, Saudi Arabia*

[3]*College of Medicine, Masaryk University, Brno, Czechia*

[4]*College of Medicine, King Khalid University, Abha, Saudi Arabia*

[5]*College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia*

[6]*College of Medicine, Hail University, Hail, Saudi Arabia*

***Corresponding Author:** Adel Hossny Hegaze, Assistant Professor, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

Received: June 16, 2020; **Published:** July 03, 2020

Abstract

Many host-specific synovial fluid biomarkers were investigated for the diagnosis of joint infections; including lactate, adenosine deaminase, calprotectin, alfa-defensin, alpha-2- macroglobulin, C-reactive protein (CRP), leukocyte esterase, and interleukin-6 (IL-6). Therefore, we aimed to systematically review the current evidence discussing the usage of synovial fluid lactate as a biomarker in the diagnosis of joint infection. The search was conducted through seven databases with the usage of the search, followed by searching the references of included papers to avoid missing relevant included papers. We included papers reporting the use of D-lactate in synovial fluid for the diagnosis of joint infections. Finally, 13 papers, with 2243 recruited patients, were included in the study. In general, the synovial lactate showed a good diagnostic value with an area under the receiver operating characteristic curve (AUC) ranging from 76% [23] to 95% [8]. The sensitivity of diagnosing joint infection ranged from 73.3% [23] to 95.7% [8], while specificity ranged from 66.7% to 96%. In conclusion, the synovial fluid lactate can be used as a screening biomarker for septic arthritis, with having the advantages of being inexpensive, needs a small volume of synovial fluid, and short turnaround time.

Keywords: *Lactate; Lactic Acid; Septic Arthritis; Joint Infection*

Introduction

Joints are essential parts of the human body that works in an orcesteric manner for maintaining the stability of the human body. Joint infection comprises a major critical issue in the world of orthopedics that needs special care once diagnosed and after treatment as well [1]. There are several routes for the inoculation of the pathologic agents for the invasion of the joint space including the transmission of the infectious agent through the bloodstream to reach the joint via the capillary-synovial membrane and introduction of the infectious agent in the surgical theatre during joint replacement [1,2].

Several risk factors were reported to induce joint infection. Berbari., *et al*. indicated that rheumatoid arthritis, steroid therapy, malignancy in general, joint malignancy, diabetes mellitus, and previous arthroplasty are potential risk factors for joint infection [3]. Bacterial

pathogens mainly staphylococcus aureus constitute the major driver of joint infection; however viral pathogens such as cytomegalovirus, Epstein bar virus, parvovirus 19 and herpes simplex virus were isolated from patients with early arthritis [3,4].

Management of joint infection is critical for patients for regaining normal joint activities. The process of management is difficult, cost-effective, and requires a team of different specialists including an orthopedic surgeon, plastic surgeon, and internist [5]. One of the essential steps in the management of joint infection is the early and proper diagnosis. Despite the presence of significant research regarding this topic, the diagnosis stills a matter of concern among orthopedics. The diagnosis is obtained from a combination of certain clinical and laboratory parameters. Patients with joint infection usually complain from joint pain, decreased joint mobility, joint erythema, and fever [1].

Laboratory investigations such as leukocytosis in complete blood picture (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were reported for the diagnosis of joint infection [6]. Moreover, certain invasive techniques can be used for proper diagnosis such as joint aspiration [7].

These diagnostic procedures faced several limitations such as non-specificity and introducing the patient for invasive maneuver. Though, recent literature have shown the usage of D-lactate biomarker for the diagnosis of joint infection. Evidence was contradicted among different studies whether it is effective or not [8-10].

Aim of the Study

We aimed to systematically review the current evidence discussing the usage of synovial fluid lactate as a biomarker in the diagnosis of joint infection.

Methods

Search strategy and study selection

Our study has followed the global recommendations of the Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA) [11]. The search was conducted through seven databases with the usage of the search term "("synovial fluid" (d lactic acid OR d-lactic acid)) AND (joint infection OR septic arthritis)". The searched databases were listed as the following: PubMed, System for Information on Grey Literature in Europe (SIGLE), Google Scholar, Web of Science (ISI), Scopus, New York Academy of Medicine (NYAM) and Virtual Health Library (VHL). We searched references from the included papers to avoid missing relevant included papers.

The inclusion criteria: We included papers reporting the use of D-lactate in synovial fluid for the diagnosis of joint infections. Publication date or language were not settled as restrictions for the inclusion criteria. The exclusion criteria: We excluded papers that used other diagnostic methods for joint infection, in addition, to duplicate papers that recruit the same patients.

Three reviewers initiated the process of title and abstract screening through an excel sheet which followed by full-text screening for collecting all relevant studies. Discussion with a senior author was developed if disagreement between the authors occurred.

Data extraction

Two authors developed an excel sheet for the extraction of relevant data from the included papers. Three reviewers extracted the data while a revision was performed by a fourth reviewer to avoid any unintentional mistakes. The discussion was done with a senior author if a disagreement occurs between the four extractors.

Quality assessment

Based on the study design of the included papers, we decided to use the Institutes of Health (NIH) quality assessment tool to determine the risk of bias for each article [12]. Three reviewers scanned each article using the risk of bias tool which consisted of fourteen questions in the case of cross-sectional and cohort studies. Quality assessment of each study was obtained through a scoring system including 14 questions. The criterion was judged as following; a score of 11 to 14 was good, 8 to 10 was fair, and studies scoring below 8 are considered of poor quality [13]. We resolved disagreement through discussion between the three reviewers.

Results

Search results

657 records were found after the systematic search of the seven databases. Excluding duplicates was done by using endnote software which resulted in 533 records for the title and abstract screening. The later resulted in 29 records for full-text screening steps. Of 29 records we included 10 studies and additional three articles were found by the manual search so we included finally thirteen studies (Figure 1).

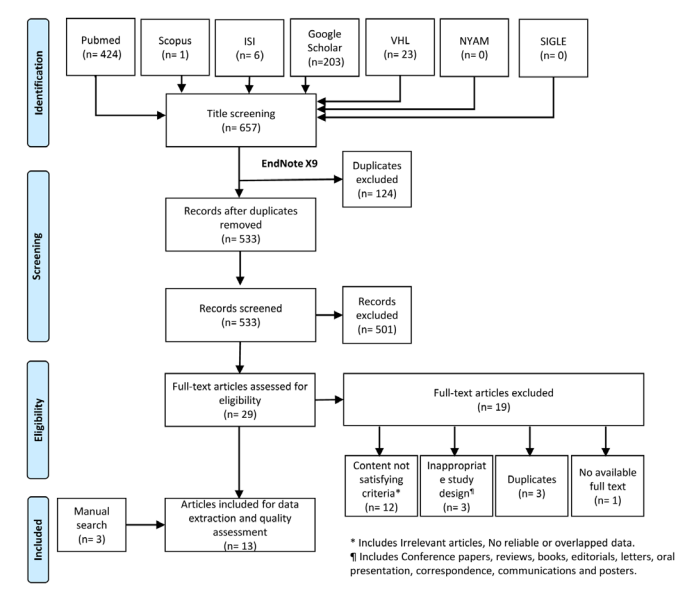

Figure 1: *PRISMA flowchart for search and screening process.*

Study characteristics and quality of the included studies

The sample size of the included studies ranged from 24 to 719 individuals. The mean male percentage was 55%, ranging from 39% to 86%. In the studies reporting lactate type, D-Lactate was the predominantly used type (Table 1).

Study	Year	Patients' Number	Male, %	Aim	Lactate Type	Main Conclusion
Karbysheva., *et al*. [8]	2020	224	45	To evaluate the performance of synovial fluid D-lactate using 2 definition criteria and determined its optimal cutoff value for diagnosing PJI.	D-lactate	The synovial fluid D-lactate showed high sensitivity (>90%) for diagnosis of PJI using both definition criteria and correlated with the pathogen virulence. The high sensitivity makes this biomarker useful as a point-of-care screening test for PJI.
Yermak., *et al*. [10]	2019	148	55	To evaluate the performance of synovial fluid D-lactate for the diagnosis of PJI and compared it with the synovial fluid leukocyte count.	D-lactate	Synovial fluid D-lactate showed similar performance to the leukocyte count for diagnosis of PJI. Advantages of D-lactate test are requirement of low synovial fluid volume, short turnaround time and low cost.
Alam., *et al*. [25]	2015	86	42	To report the determination of lactate in synovial fluids of male and female arthritis patients, to differentiate between presence of sepsis or bacterial infectious arthritis and non-infectious ones.	L-Lactate	It is suggested that lactate determination should be included in chemical analysis of synovial fluids, when arthritis patients were suspected of sepsis or synovium bacterial infections.
Lenski., *et al*. [23]	2015	719	NA	To investigate which markers in serum and in the synovial fluid have the highest diagnostic potential for predicting septic arthritis and PJIs.	NA	The use of the corresponding interval likelihood ratios could help physicians to estimate the probability of septic arthritis and PJI more accurately
Lenski., *et al*. [22]	2014	82	57	To investigate which inflammatory markers allow an accurate differentiation of septic and gouty arthritis.	NA	Lactate in the synovial fluid has excellent diagnostic potential to differ septic arthritis from gouty arthritis. Synovial lactate levels above 10 mmol/L almost proofed septic arthritis, lactate levels lower than 4.3 mmol/L make it very unlikely.
Gratacós., *et al*. [26]	1995	119	NA	To analyze the usefulness of D-lactic acid levels in synovial fluid (SF) as a rapid test to support the early diagnosis of bacterial arthritis (BA)	D-lactate	D-lactic acid is an accurate, easy test that can be carried out in any laboratory, to support the early diagnosis of BA.
Kortekangas., *et al*. [27]	1994	24	NA	To evaluate the use of D-lactic acid in differential diagnosis of bacterial arthritis.	D-lactate	Determination of SF D-lactic acid is not useful in differential diagnosis of bacterial arthritis.

Marcos., *et al*. [16]	1991	310	NA	To investigate the value of determining D-lactate concentrations in body fluids for the rapid diagnosis of bacterial infections	D-lactate	The measurement of D-lactate concentration in body fluids offers a rapid (2-hour) and useful method of differentiating between infectious and non-infectious body fluid diseases.
Arthur., *et al*. [28]	1983	41	39	To determine lactic acid levels by the lactic dehydrogenase method in synovial fluid of patients with various rheumatic diseases, to test the concept that significantly elevated values were diagnostic of septic arthritis.	NA	Could not differentiate septic arthritis from RA on the basis of synovial fluid lactic acid levels.
Curtis., *et al*. [29]	1983	283	63	To assess the value of synovial fluid lactate estimation in the diagnosis of septic arthritis.	NA	The predictive value of a negative result was 98 per cent and the value of the test appeared to be in the rapid exclusion of sepsis in untreated patients.
Riordan., *et al*. [19]	1982	52	NA	To assess the value of synovial fluid lactate estimation in the differentiating between septic and non-septic arthritis.	NA	Lactic acid was found to be a useful and rapid test for differentiating between septic and non-septic arthritis being markedly raised (> 12 mmol/l) in all the septic joints. Raised lactic acid concentrations were of particular diagnostic value in patients in whom antibiotic therapy had commenced before joint aspiration. The results of lactic acid estimation on sequential samples were helpful in assessing the response of septic arthritis to treatment.
Mossman., *et al*. [30]	1981	71	NA	To assess the value of synovial fluid lactate estimation in the differentiating between septic and non-septic arthritis.	NA	The enzyme method of lactic acid estimation is an accurate reproducible means of differentiating septic from nonseptic arthritis prior to the isolation of the infecting organism. However, caution is necessary when interpreting the results in those patients who have recently received antibiotic therapy, or in whom gonococcal arthritis is suspected.
Brook., *et al*. [31]	1978	84	86	To study synovial fluid lactic acid concentrations in 84 cases of acute, monoarticular arthritis to see if this test could be of value in the rapid diagnosis of septic arthritis.	NA	With the proper equipment, determination of lactic acid can be a relatively rapid, reliable procedure. Synovial fluid lactic acid concentrations therefore can be used as a rapid, supplemental diagnostic aid in differentiating nongonococcal septic arthritis from both gonococcal and nonseptic acute arthritis.

Table 1: *Characteristics of included studies. PJI: Periprosthetic Joint Infection.*

Four studies were of good quality, seven of fair quality and two were of poor quality (Table 2) [8,10,14-24]. The most defective aspects included blinding of outcome assessors, loss to follow up, a participation rate of eligible persons, sample size justification/power description, sufficient timeframe and exposure(s) assessed more than once.

Study	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Total score	Judgement
Karby-sheva., *et al*. [8]	2020	1	1	1	1	1	1	1	1	1	0	1	0	0	1	11	Good
Yermak., *et al*. [10]	2019	1	1	0	1	0	1	0	0	0	0	1	0	0	0	5	Poor
Alam., *et al*. [25]	2015	1	1	1	1	0	1	1	1	1	0	1	0	0	0	9	Fair
Lenski., *et al*. [23]	2015	1	1	1	1	0	1	1	1	1	0	1	0	0	0	9	Fair
Lenski., *et al*. [22]	2014	1	1	1	1	1	1	1	1	1	0	1	0	0	1	11	Good
Gratacós., *et al*. [26]	1995	1	1	1	1	1	1	1	0	1	0	1	0	0	1	10	Good
Kortekan-gas., *et al*. [27]	1994	1	1	1	1	1	1	1	0	1	0	1	0	0	1	10	Good
Marcos., *et al*. [16]	1991	1	1	0	1	0	1	0	0	0	0	1	0	0	0	5	Poor
Arthur., *et al*. [28]	1983	1	1	0	1	0	1	0	1	1	1	1	0	0	0	8	Fair
Curtis., *et al*. [29]	1983	1	1	0	1	0	1	0	1	1	1	1	0	0	0	8	Fair
Riordan., *et al*. [19]	1982	1	1	0	1	0	1	0	1	1	1	1	0	0	0	8	Fair
Mossman., *et al*. [30]	1981	1	1	0	1	0	1	0	1	1	1	1	0	0	0	8	Fair
Brook., *et al*. [31]	1978	1	1	0	1	0	1	0	1	1	1	1	0	0	0	8	Fair

Table 2: *Quality assessment of the included studies.*

Q1. Was the research question or objective in this paper clearly stated?; Q2. Was the study population clearly specified and defined?; Q3. Was the participation rate of eligible persons at least 50%?; Q4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? Q5. Was a sample size justification, power description, or variance and effect estimates provided?; Q6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?; Q7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?; Q8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?; Q9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; Q10. Was the exposure(s) assessed more than once over time?; Q11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; Q12. Were the outcome assessors blinded to the exposure status of participants?; Q13. Was loss to follow-up after baseline 20% or less?; Q14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Lactate concentrations in synovial fluid

Table 3 shows a comparison of lactate concentrations in synovial fluid of septic and aseptic arthritis. Most of the included studies showed significant differences in lactate concentration between the aforementioned groups, whether periprosthetic joint infection (PJI) versus aseptic arthritis [8,10] or septic arthritis versus aseptic arthritis [22,27,31]. However, one study did not show any significant difference (P > 0.1) between septic arthritis versus aseptic arthritis (Inflammatory and non-inflammatory) [28].

Study	Year	Comparison Groups	Specimens No.	Lactate Type	Expression	Septic Group	Aseptic Group	P-value of the difference
Karbysheva., *et al*. (MSIS Criteria) [8]	2020	PJI Vs. AF	71 + 153	D-lactate	Median (interquartile range), mmol/L	PJI: 2.6 (1.9-2.9)	AF: 0.7 (0.4-1.2)	P < 0.0001
Karbysheva., *et al*. (Institutional Criteria) [8]	2020	PJI Vs. AF	92 + 132	D-lactate	Median (interquartile range), mmol/L	PJI: 2.4 (1.8-2.9)	AF: 0.7 (0.3-1.0)	P < 0.001
Yermak., *et al*. [10]	2019	PJI Vs. AF	38 + 19	D-lactate	Mean, mmol/L	PJI: 1.40	AF: 0.915	P < 0.001
Lenski., *et al*. [23]	2015	PJI Vs. AF	67 + 36	NA	Mean (standard deviation), mmol/L	PJI: 8.9 (5.5)	AF: 5.3 (5.6)	NA
Lenski., *et al*. [22]	2014	IA Vs. GA	38+22	NA	Mean (range), mmol/L	IA: 11.7 (0.2-48.0)	GA: 3.5 (1.5-7.9)	P = 0.00003
Kortekangas., *et al*. [27]	1994	IA Vs. AF	7 + 16	D-lactate	Median (range), mmol/L	IA: 0.20 (0.05-1.63)	AF: 0.05 (0-0.24)	P =0.0056
Arthur., *et al*. [28]	1983	IA Vs. AF (Inflammatory)	9 + 26	NA	Mean ± standard deviation, mg/dl	IA: 53.6 ± 13.8	AF: 43.4 ± 7.2	P > 0.1
		IA Vs. AF (Non-inflammatory)	9 + 6	NA	Mean ± standard deviation, mg/dl	IA: 53.6 ± 13.8	AF: 24.4 ± 3.7	P > 0.1
Curtis., *et al*. [29]	1983	IA Vs. AF	9 + 75	NA	Mean ± standard deviation, mmol/L	IA: 11.6 ± 4.0	AF: 1.9 ± 0.7	NA
			10* + 75		Mean ± standard deviation), mmol/L	IA: 9.1 ± 3.4		

Riordan., *et al*. [19]	1982	IA (Culture Positive) Vs. Rheumatoid arthritis	11 + 18	NA	Mean ± SEM, mmol/L	24.4 ± 3.0	5.9 ± 0.9	NA
		IA (Culture Positive) Vs. Non-specific inflammatory	11 + 11		Mean ± SEM, mmol/L		3.9 ± 0.6	
		IA (Culture Positive) Vs. Degenerative (Crystals)	11 + 5		Mean ± SEM, mmol/L		2.7 ± 0.4	
		IA (Culture Positive) Vs. Degenerative (Osteoarthritis)	11 + 3		Mean ± SEM, mmol/L		1.8 ± 0.2	
Mossman., *et al*. [30]	1981	IA Vs. AF	12 + 63	NA	mmol/L	IA: ≥ 11	AF: ≤ 10.2	NA
Brook., *et al*. [31]	1978	IA (nongonococcal) Vs. AF	27 + 45	NA	Mean (range), mg/100ml	IA : 1170 (48-2500)	AF: 34 (5-62)	P < 0.001
		IA (gonococcal) Vs. AF	12 + 45			IA: 27 (18-50)		NA

Table 3: *Comparison of lactate concentrations in synovial fluid of septic and aseptic arthritis. MSIS: Musculoskeletal Infection Society Criteria; PJI: Periprosthetic Joint Infection; AF: Aseptic Failure/Arthritis; IA: Infectious/Septic Arthritis; GA: Gouty Arthritis; * Partially treated; SEM, Standard Error of the Mean.*

Diagnostic accuracy of the synovial lactate

In the included studies, a total of 855 specimens were collected from synovial fluids of patients with septic arthritis; 509 from patients with PJI and 346 from patients with septic arthritis. The majority of the studies [8,10,16,26] reported measuring D-type of synovial lactate, while two studies [22,23] did not report the exact type (Table 4).

In general, the synovial lactate showed a good diagnostic value with an area under the receiver operating characteristic curve (AUC) ranging from 76% [23] to 95% [8]. The sensitivity of diagnosing joint infection ranged from 73.3% [23] to 95.7% [8], while specificity ranged from 66.7% to 96%. The full diagnostic performance measures are summarized in table 4.

Study	Year	Condition	Specimens No.	Lactate Type	AUC, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	NPV, % (95% CI)	PPV, % (95% CI)	LR+ (95% CI)	LR– (95% CI)	Cut-off Value
Karbysheva., *et al*. [8]	2020											
Musculoskeletal Infection Society criteria												
>1.2		PJI	68	D-lactate	93 (89-96)	95.7 (88.1-99.1)	74.5 (66.8-81.2)	97.4 (92.7-99.4)	63.6 (53.7-72.6)	3.7 (3.4-4.2)	0.05 (0.02-0.2)	>1.2 mmol/L
>1.3		PJI	67	D-lactate	93 (89-96)	94.3 (86.2-98.4)	78.4 (71.1-84.7)	96.8 (91.9-99.1)	67.0 (56.9-76.1)	4.3 (4.0-4.8)	0.07 (0.03-0.2)	>1.3 mmol/L

>1.4		PJI	63	D-lactate	93 (89-96)	88.7 (79.0-95.0)	79.4 (72.5-85.8)	93.8 (88.2-97.3)	67.0 (56.5-76.4)	4.3 (3.9-4.9)	0.1 (0.07-0.3)	>1.4 mmol/L
Institutional Criteria												
>1.2		PJI	87	D-lactate	95 (93-98)	94.6 (87.8-98.2)	84.8 (77.6-90.5)	95.7 (90.3-98.6)	79.4 (70.5-86.6)	6.2 (5.7-6.8)	0.06 (0.02-0.2)	>1.2 mmol/L
>1.3		PJI	85	D-lactate	95 (93-98)	92.4 (84.9-96.9)	88.6 (81.9-93.5)	94.4 (88.7-97.7)	85.0 (76.5-91.3)	8.1 (7.5-8.8)	0.08 (0.04-0.2)	>1.3 mmol/L
>1.4		PJI	79	D-lactate	95 (93-98)	85.8 (77.0-92.2)	88.6 (76.7-89.7)	90.0 (83.5-94.6)	84.0 (75.0-90.8)	7.5 (6.8-8.4)	0.1 (0.08-0.3)	>1.4 mmol/L
Yermak., *et al.* [10]	2019	PJI	38	D-lactate	90.3 (85.7-95.0)	86.4 (75.0-95.5)	81.7 (74.0-88.5)	93.5 (88.7-97.5)	66.7 (57.8-76.6)	4.72	0.17	1.263 mmol/L
Lenski., *et al.* [23]	2015	IA	152	NA	76.0 (65.3-86.7)	78.1 (61.3-89.0)	66.7 (57.8-74.5)	-	-	2.34 (1.72-3.20)	0.33 (0.17-0.64)	5.2 mmol/L
		PJI	22	NA	76.0 (48.4-92.7)	73.3 (48.1-89.1)	66.7 (30.0-90.3)	-	-	2.20 (0.68-7.10)	0.40 (0.15-1.10)	5.3 mmol/L
Lenski., *et al.* [22]	2014	IA	38	NA	90.1 (82.3-97.9)	89.5 (75.9-95.8)	77.3 (56.6-89.9)	-	-	3.94 (1.81-8.57)	0.14 (0.05-0.35)	4.3 mmol/L
Gratacós., *et al.* [26]	1995	IA	99	D-lactate	-	85	96	97	81	-	-	0.05 mM
Marcos., *et al.* [16]	1991	IA	57	D-lactate	-	90	87	97	60	-	-	0.05 mM

Table 4: *Summary of reported diagnostic performance of synovial fluid D-lactate.*

PJI: Periprosthetic Joint Infection; IA: Infectious/Septic Arthritis; AUC: Area Under the Receiver Operating Characteristic Curve; PPV: Positive Predictive Value; NPV, Negative Predictive Value; LR+: Positive Likelihood Ratio; LR -: Negative Likelihood Ratio; 95% CI: 95% Confidence Interval.

Discussion

Through the past years, many host-specific synovial fluid biomarkers were investigated for the diagnosis of septic arthritis, including adenosine deaminase, calprotectin, alfa-defensin, alpha-2- macroglobulin, C-reactive protein (CRP), leukocyte esterase, and interleukin-6

(IL-6) [32-35]. Nevertheless, these biomarkers can be high in aseptic conditions when the synovial fluid has a high leukocyte count; including crystal-induced arthritis, inflammation following trauma, or rheumatic arthritis. This urged the need for a pathogen-specific biomarker, like lactate, which was the rationale for conducting this study.

The current study is a systematic review of all studies assessing the ability of lactate to diagnose septic arthritis and to differentiate it from a septic one. In general, the studies showed high sensitivity and moderate specificity; making it a good candidate to act as a biomarker for the diagnosis/exclusion of septic arthritis. Moreover, the lactate assay would be of great diagnostic value in patients who commenced an antibiotic therapy prior to joint aspiration. Furthermore, a sequential measurement of the synovial fluid lactate would be helpful to assess patients' response to treatment. It can be done with a low cost and small amount of synovial fluid.

Gratacos., *et al*. [26] reported good diagnostic value of D-lactate (AUC = 90%), with high specificity (96%) and sensitivity (86%) when a 0.05 mmol/L cutoff value was used, Kortekangas., *et al*. [27] showed that the measurements of synovial fluid D-lactate concentrations were significantly higher in individuals with septic arthritis when compared with the ones with extra-articular infections (P = 0.006). In a more recent study from [10], the value of synovial fluid D-lactate in the diagnosis of PJI, in 148 patients, was evaluated; showing a sensitivity of 86.4% and specificity of 80.8%, based on the institutional definition criteria of PJI. Investigation the optimal cut-off value for the D-lactate concentration, 1.3 mmol/L found to be the best, with sensitivity > 90% using both institutional definition criteria and Musculoskeletal Infection Society criteria [8].

The performance of the synovial lactate sounds to be superior/comparable to other used biomarkers. The synovial white blood cell count was inferior to lactate in terms of sensitivity (36% to 100%); however, it showed comparable results in terms of specificity (80% to 99%) [36,37]. Similar to lactate assays, white blood cell count can be done in an outpatient setting and not affected by antimicrobial therapy [38]. Another used biomarker is the synovial leukocyte esterase, which showed a good diagnostic value with a sensitivity of 66% to 100% and specificity of 77% to 100% [39-41]. Nevertheless, the contamination of the sample with blood or other debris would make it impossible to read the reagent strip adequately [38]. In the same context, an emerging synovial biomarker is the alpha-defensin; Showing a very high sensitivity (95.5% to 100%) and specificity (95% - 100%). This biomarker is showing promising results and does not seem to be affected by a prior antibiotic therapy; however, it is high in cost and not readily available in every hospital [38].

There are two other biomarkers that could be assayed through blood or synovial fluid samples. The first one is the IL-6, which showed a better performance in samples of synovial fluid, with a sensitivity of 62.5% to 97% and specificity of 85.7% to100% [42-46]. The advantage of this test is being expensive and not available in every hospital [38]. The second one is the CRP, which showed a reasonable diagnostic value with a sensitivity of 70% to 97.3% and specificity of 78.6% to 100% [47-52]. The biggest advantage of CRP is being a non-specific marker of inflammation so, an accurate history taking and examination should be done prior to interpreting its results [38].

The current study has some limitations related to the nature of the included studies. Some studies did not report the type of the synovial lactate measured nor the exact case definition or diagnostic criteria used. Moreover, some studies had a relatively small sample size and heterogeneous conditions of arthritis.

Conclusion

The synovial fluid lactate can be used as a screening biomarker of high sensitivity to diagnose septic arthritis. It has comparable performance to the other synovial biomarkers, with having the advantages of being inexpensive, needs a small volume of synovial fluid, and short turnaround time.

Funding

None.

Conflicts of Interest

No conflicts related to this work.

Bibliography

1. Bowman Erik and Justin Siebler. "Septic Arthritis". Orthopedic Surgery Clerkship: A Quick Reference Guide for Senior Medical Students. Editions. Eltorai, Adam E. M., Craig P. Eberson and Alan H. Daniels. Cham: Springer International Publishing (2017): 703-706.

2. Tande Aaron J and Robin Patel. "Prosthetic Joint Infection". *Clinical Microbiology Reviews* 27.2 (2014): 302-345.

3. Berbari Elie F., *et al*. "Risk Factors for Prosthetic Joint Infection: Case-Control Study". *Clinical Infectious Diseases* 27.5 (1998): 1247-1254.

4. Stahl Hans-Detlev., *et al*. "Detection of Multiple Viral DNA Species in Synovial Tissue and Fluid of Patients with Early Arthritis". *Annals of the Rheumatic Diseases* 59.5 (2000): 342-346.

5. Osmon Douglas R., *et al*. "Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America". *Clinical Infectious Diseases* 56.1 (2013): e1-e25.

6. Kapadia Bhaveen H., *et al*. "Periprosthetic Joint Infection". *The Lancet* 387.10016 (2016): 386-394.

7. Schinsky Mark F., *et al*. "Perioperative Testing for Joint Infection in Patients Undergoing Revision Total Hip Arthroplasty". *Journal of Bone and Joint Surgery* 90.9 (2008): 1869-1875.

8. Karbysheva Svetlana., *et al*. "Synovial Fluid D-Lactate–a Novel Pathogen-Specific Biomarker for the Diagnosis of Periprosthetic Joint Infection". *The Journal of Arthroplasty* (2020).

9. Robinson Claire S., *et al*. "Are Serum Amyloid a or D-Lactate Useful to Diagnose Synovial Contamination or Sepsis in Horses?" *The Veterinary Record* 181.16 (2017): 425.

10. Yermak Katsiaryna., *et al*. "Performance of Synovial Fluid D-Lactate for the Diagnosis of Periprosthetic Joint Infection: A Prospective Observational Study". *Journal of Infection* 79.2 (2019): 123-129.

11. Liberati A., *et al*. "The Prisma Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration". *Plos Medicine* 6.7 (2009): 28.

12. National Heart Lung and Blood Institute. "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies". Bethesda: National Institutes of Health, Department of Health and Human Services (2014): 103-111.

13. Leung Amy., *et al*. "A Systematic Review of Patient-Related Risk Factors for Catheter-Related Thrombosis". *Journal of Thrombosis and Thrombolysis* 40.3 (2015): 363-373.

14. Mehmood Khalid. "Estimation of Lactate (Lactic Acid) in Synovial Fluid of Arthritis Patients for Differential Diagnosis of Septic Arthritis".

15. Kortekangas P., *et al*. "Synovial-Fluid D-Lactic Acid in Bacterial and Other Acute Joint Effusions". *Scandinavian Journal of Rheumatology* 23.4 (1994): 203-205.

16. Marcos MA., *et al*. "Determination of D-Lactate Concentration for Rapid Diagnosis of Bacterial Infections of Body Fluids". *European Journal of Clinical Microbiology and Infectious Diseases* 10.11 (1991): 966-969.

17. Brook Itzhak., *et al*. "Synovial Fluid Lactic Acid. A Diagnostic Aid in Septic Arthritis". *Arthritis and Rheumatism: Official Journal of the American College of Rheumatology* 21.7 (1978): 774-779.

18. Eugene Arthur R., *et al*. "Synovial Fluid Lactic Acid in Septic and Nonseptic Arthritis". *Arthritis and Rheumatism: Official Journal of the American College of Rheumatology* 26.12 (1983): 1499-1505.

19. Riordan T., *et al*. "Synovial Fluid Lactic Acid Measurement in the Diagnosis and Management of Septic Arthritis". *Journal of Clinical Pathology* 35.4 (1982): 390-394.

20. Curtis GDW., *et al.* "Synovial Fluid Lactate and the Diagnosis of Septic Arthritis". *Journal of Infection* 6.3 (1983): 239-246.

21. Gratacos J., *et al*. "D-Lactic Acid in Synovial Fluid. A Rapid Diagnostic Test for Bacterial Synovitis". *The Journal of Rheumatology* 22.8 (1995): 1504-1508.

22. Lenski Markus and Michael A Scherer. "Analysis of Synovial Inflammatory Markers to Differ Infectious from Gouty Arthritis". *Clinical Biochemistry* 47.1-2 (2014): 49-55.

23. Markus Lenski., *et al*. "Diagnostic Potential of Inflammatory Markers in Septic Arthritis and Periprosthetic Joint Infections: A Clinical Study with 719 Patients". *Infectious Diseases* 47.6 (2015): 399-409.

24. Mossman SS., *et al*. "Synovial Fluid Lactic Acid in Septic Arthritis". *The New Zealand Medical Journal* 93.678 (1981): 115-117.

25. Alam Junaid., *et al*. "Estimation of Lactate (Lactic Acid) in Synovial Fluid of Arthritis Patients for Differential Diagnosis of Septic Arthritis". *International Journal of Biological and Biomedical Sciences* 4.6 (2015): 053-054.

26. Gratacós J., *et al*. "D-Lactic Acid in Synovial Fluid. A Rapid Diagnostic Test for Bacterial Synovitis". *The Journal of Rheumatology* 22.8 (1995): 1504-1508.

27. Kortekangas P., *et al*. "Synovial-Fluid D-Lactic Acid in Bacterial and Other Acute Joint Effusions". *Scandinavian Journal of Rheumatology* 23.4 (1994): 203-205.

28. Arthur RE., *et al*. "Synovial Fluid Lactic Acid in Septic and Nonseptic Arthritis". *Arthritis Rheum* 26.12 (1983): 1499-1505.

29. Curtis GD., *et al*. "Synovial Fluid Lactate and the Diagnosis of Septic Arthritis". *Journal of Infection* 6.3 (1983): 239-246.

30. Mossman SS., *et al*. "Synovial Fluid Lactic Acid in Septic Arthritis". *The New Zealand Medical Journal* 93.678 (1981): 115-117.

31. Brook I., *et al*. "Synovial Fluid Lactic Acid. A Diagnostic Aid in Septic Arthritis". *Arthritis and Rheumatology* 21.7 (1978): 774-779.

32. Sousa R., *et al*. "Improving the Accuracy of Synovial Fluid Analysis in the Diagnosis of Prosthetic Joint Infection with Simple and Inexpensive Biomarkers: C-Reactive Protein and Adenosine Deaminase". *The Bone and Joint Journal* 99-b.3 (2017): 351-357.

33. Wouthuyzen-Bakker M., *et al*. "Synovial Calprotectin: An Inexpensive Biomarker to Exclude a Chronic Prosthetic Joint Infection". *The Journal of Arthroplasty* 33.4 (2018): 1149-1153.

34. Renz N., *et al*. "Alpha Defensin Lateral Flow Test for Diagnosis of Periprosthetic Joint Infection: Not a Screening but a Confirmatory Test". *Journal of Bone and Joint Surgery American* 100.9 (2018): 742-750.

35. Shafafy R., *et al*. "Use of Leucocyte Esterase Reagent Strips in the Diagnosis or Exclusion of Prosthetic Joint Infection". *The Bone and Joint Journal* 97-b.9 (2015): 1232-1236.

36. Simonsen L., *et al*. "White Blood Cell Scintigraphy for Differentiation of Infection and Aseptic Loosening: A Retrospective Study of 76 Painful Hip Prostheses". *Acta Orthopaedica* 78.5 (2007): 640-647.

37. Mason J Bohannon., *et al*. "The Value of White Blood Cell Counts before Revision Total Knee Arthroplasty". *The Journal of Arthroplasty* 18.8 (2003): 1038-1043.

38. Vasoo S., *et al*. "Evaluation of the Film array Blood Culture Id Panel on Biofilms Dislodged from Explanted Arthroplasties for Prosthetic Joint Infection Diagnosis". *Journal of Clinical Microbiology* 53.8 (2015): 2790-2792.

39. Wetters Nathan G., *et al*. "Leukocyte Esterase Reagent Strips for the Rapid Diagnosis of Periprosthetic Joint Infection". *The Journal of Arthroplasty* 27.8 (2012): 8-11.

40. Goswami K., *et al*. "Current Recommendations for the Diagnosis of Acute and Chronic Pji for Hip and Knee-Cell Counts, Alpha-Defensin, Leukocyte Esterase, Next-Generation Sequencing". *Current Reviews in Musculoskeletal Medicine* 11.3 (2018): 428-438.

41. Signore Alberto., *et al*. "Consensus Document for the Diagnosis of Prosthetic Joint Infections: A Joint Paper by the Eanm, Ebjis, and Esr (with Escmid Endorsement)". *European Journal of Nuclear Medicine and Molecular* Imaging 46.4 (2019): 971-988.

42. Elgeidi A., *et al*. "Interleukin-6 and Other Inflammatory Markers in Diagnosis of Periprosthetic Joint Infection". *International Orthopaedics* 38.12 (2014): 2591-2595.

43. Hoell S., *et al*. "Interleukin-6 in Two-Stage Revision Arthroplasty: What Is the Threshold Value to Exclude Persistent Infection before Re-Implanatation?" *The Bone and Joint Journal* 97-b.1 (2015): 71-75.

44. Bottner F., *et al*. "Interleukin-6, Procalcitonin and Tnf-Alpha: Markers of Peri-Prosthetic Infection Following Total Joint Replacement". *The Journal of Bone and Joint Surgery British* 89.1 (2007): 94-99.

45. Di Cesare PE., *et al*. "Serum Interleukin-6 as a Marker of Periprosthetic Infection Following Total Hip and Knee Arthroplasty". *Journal of Bone and Joint Surgery American* 87.9 (2005): 1921-1927.

46. Lenski Markus and Michael A Scherer. "Synovial Il-6 as Inflammatory Marker in Periprosthetic Joint Infections". *The Journal of Arthroplasty* 29.6 (2014): 1105-1109.

47. Omar M., *et al*. "Synovial C-Reactive Protein as a Marker for Chronic Periprosthetic Infection in Total Hip Arthroplasty". *The Bone and Joint Journal* 97-b.2 (2015): 173-176.

48. Fink B., *et al*. "The Value of Synovial Biopsy, Joint Aspiration and C-Reactive Protein in the Diagnosis of Late Peri-Prosthetic Infection of Total Knee Replacements". *The Journal of Bone and Joint Surgery British* 90.7 (2008): 874-878.

49. Greidanus NV., *et al*. "Use of Erythrocyte Sedimentation Rate and C-Reactive Protein Level to Diagnose Infection before Revision Total Knee Arthroplasty. A Prospective Evaluation". *Journal of Bone and Joint Surgery American* 89.7 (2007): 1409-1416.

50. Parvizi J., *et al*. "Mark B. Coventry Award: Synovial C-Reactive Protein: A Prospective Evaluation of a Molecular Marker for Periprosthetic Knee Joint Infection". *Clinical Orthopaedics and Related Research* 470.1 (2012): 54-60.

51. Tetreault MW., *et al*. "Is Synovial C-Reactive Protein a Useful Marker for Periprosthetic Joint Infection?" *Clinical Orthopaedics and Related Research* 472.12 (2014): 3997-4003.

52. Deirmengian C., *et al*. "Combined Measurement of Synovial Fluid A-Defensin and C-Reactive Protein Levels: Highly Accurate for Diagnosing Periprosthetic Joint Infection". *Journal of Bone and Joint Surgery American* 96.17 (2014): 1439-1445.

Volume 16 Issue 8 August 2020