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ENVIRONMENTAL STRESS-INDUCED OXIDATIVE DAMAGE AND MOLECULAR BIOMARKERS: A BIOTECHNOLOGICAL APPROACH FOR ASSESSING ENVIRONMENTAL HEALTH RISKS

Emaan Zehra[*1], Muhabbat Hussain[2], Amina Zehra[3], Roshan Zehra[4], Zeeshan Haider[5]

[*1]*M.Phil. Scholar, Department of Biotechnology Muhammad Ali Jinnah University, Karachi, Pakistan*
[2]*School of Software Engineering, Dalian University of Technology, Dalian 116024, China*
[3]*Department of Physics, Karakoram International University (KIU), Gilgit-Baltistan, Pakistan, Pakistan*
[4]*Department of Biology, University of Karachi, Karachi, Pakistan*
[5]*Department of Computer Science, Dawood University of Engineering & Technology, Karachi, Pakistan*

[*1]emaanhussain110@gmail.com, [2]muhabbathussain@mail.dlut.edu.cn, [3]aminazehra43@gmail.com , [4]roshanzehra1214@gmail.com, [5]zeeshanhaiderrajuwa@gmail.com

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Corresponding Author: *
Emaan Zehra

Abstract

Osteoarthritis (OA) and rheumatoid arthritis (RA) are common joint disorders driven by distinct but overlapping pathophysiological mechanisms, including altered bone turnover and oxidative stress. Alkaline phosphatase (ALP), an enzyme central to bone mineralization, and malondialdehyde (MDA), a byproduct of lipid peroxidation and marker of oxidative stress, are potential biochemical indicators of disease activity in arthritis. To evaluate and compare serum ALP and MDA levels in patients with OA and RA against healthy controls, and to explore their potential clinical utility as adjunct biomarkers. In this cross-sectional study, 41 female patients (35 with OA, aged 40–70 years, and 6 with RA, aged 20–30 years) attending the orthopedic outpatient department of a local hospital were recruited between June and August 2023, along with 15 age-matched healthy controls. Diagnosis was confirmed by clinical history, physical examination, and radiological assessment. Serum ALP activity was measured by the IFCC/DGKC kinetic p-nitrophenylphosphate method, and serum MDA was quantified by the thiobarbituric acid reactive substances (TBARS) assay. The mean serum ALP activity was markedly higher in OA/RA patients (109.83 ± 246.88 U/L) than in controls (60.33 ± 36.06 U/L). Similarly, mean serum MDA levels were substantially elevated in patients (230.14 ± 163.89 nM/mL) compared with controls (43.54 ± 28.53 nM/mL). The majority of patients were diagnosed with OA (85.4%), were aged 20–40 years (53.7%), and were managed with medication (90.2%). Both ALP and MDA are elevated in patients with OA and RA relative to healthy individuals, reflecting increased bone turnover and heightened oxidative stress. These findings support the potential value of ALP and MDA as complementary biochemical markers for assessing disease activity, monitoring progression, and evaluating treatment response in arthritis, although their routine clinical adoption will require validation in larger, longitudinal cohorts.

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INTRODUCTION

Alkaline phosphatase (ALP) has, since the late 1970s, been among the most frequently requested enzyme assays in clinical medicine, owing largely to its central role in the detection, monitoring, and investigation of skeletal disorders (1–3). ALP was first characterized by Robison in 1923, who observed that bone extracts—but not non-ossifying cartilage—could hydrolyze a hexose phosphoric ester and liberate inorganic phosphate, a finding that established the enzyme's role in promoting skeletal mineralization (4–6).

ALP exists as a homodimeric metalloenzyme, with each catalytic site coordinating two zinc ions and one magnesium ion essential for hydrolysis of phosphate monoesters (7). At least four tissue-specific human isoforms have been described—placental, intestinal, liver/bone/kidney (tissue-nonspecific), and germ-cell ALP—each encoded by distinct gene loci and distinguishable by structural, biochemical, and immunological methods (8–10). The bone-specific isoform, tissue-nonspecific alkaline phosphatase (TNAP), is anchored to the outer osteoblast membrane and facilitates hydroxyapatite deposition by hydrolyzing inorganic pyrophosphate, a potent inhibitor of mineralization (11–15). Clinically, elevated ALP is associated with a broad range of conditions, including osteoplastic bone tumors, osteomalacia, osteoporosis, hepatobiliary disease, Paget's disease, hyperparathyroidism, and pregnancy, while reduced levels occur in hypophosphatemia, malnutrition, and several endocrine and hematologic disorders (16–24).

Arthritis, derived from the Greek for "joint disease," encompasses a group of disorders characterized by joint inflammation, pain, stiffness, and progressive structural damage. Osteoarthritis (OA), the most common form, is defined by focal cartilage degeneration, subchondral bone remodeling, osteophyte formation, and variable synovial inflammation, and predominantly affects the knee, hip, hand, and spine (25–31). Rheumatoid arthritis (RA), in contrast, is a systemic autoimmune disease characterized by chronic synovial inflammation with the potential to damage the heart, lungs, kidneys, and other organs beyond the joints (34–36). The 2010 ACR/EULAR classification criteria for RA incorporate joint involvement, serological markers (rheumatoid factor and anti-citrullinated protein antibody), acute-phase reactants, and symptom duration to enable earlier diagnosis (37, 38). In both OA and RA, ALP is frequently elevated, plausibly reflecting increased osteoplastic activity, subchondral bone remodeling, or synovial inflammation, although the precise source of this elevation remains incompletely understood (39, 40).

Oxidative stress—an imbalance between the production of reactive oxygen species (ROS) and their neutralization by enzymatic (catalase, glutathione peroxidase, superoxide dismutase) and non-enzymatic (vitamins A, C, and E) antioxidant systems—is increasingly recognized as a contributor to the pathogenesis of chronic inflammatory joint disease (41–44). Excess ROS promote lipid peroxidation, protein carbonylation, and DNA damage, processes that can exacerbate synovial inflammation, accelerate cartilage degradation, and impair antioxidant defenses in both OA and RA (52). Malondialdehyde (MDA), a stable end-product of lipid peroxidation, is a widely used surrogate marker of oxidative stress, and elevated serum MDA has been reported in patients with RA and OA, potentially reflecting the extent of tissue damage and disease activity (52, 53).

Despite growing interest in both markers individually, the relationship between ALP and MDA levels and arthritis, relative to healthy individuals, remains inadequately characterized, and few studies have examined them concurrently in the same patient cohort. This study was therefore designed to measure and compare serum ALP and MDA levels in patients with OA and RA against healthy controls, with the aim of clarifying their potential utility as complementary biomarkers of disease activity, bone turnover, and oxidative stress in arthritis.

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Materials and Methods

Study design and participants

This cross-sectional study was conducted in the Department of Biochemistry, University of Karachi, between June and August 2023. Forty-one female patients were recruited from the orthopedic outpatient department (OPD) of a local hospital: 35 patients diagnosed with OA (aged 40–70 years) and 6 patients diagnosed with RA (aged 20–30 years). Diagnoses were confirmed through comprehensive medical history, physical examination, and radiological assessment, and patients were enrolled irrespective of disease duration, activity, or treatment history. Fifteen age-appropriate healthy volunteers were recruited as controls for comparison of ALP and MDA levels.

Inclusion criteria required participants to have maintained stable dietary habits, including Vitamin D and calcium supplementation, for the preceding three months, with OA/RA diagnoses corroborated by laboratory tests and radiography; female participants were required to be in the peri- or post-menopausal stage. Participants with a history of alcohol or tobacco use, hypertension, diabetes mellitus, joint trauma, thyroid dysfunction, hepatic or renal disease, coronary heart disease, obesity, prior anti-inflammatory drug use, or antioxidant supplementation were excluded.

Sample collection

A 5 mL venous blood sample was drawn from the antecubital vein of each participant under aseptic conditions and collected into a clotting-activator tube. Samples were labeled with unique identification codes, transported on ice, and centrifuged at 2500 rpm for 10 minutes. Serum was separated into Eppendorf tubes and stored at −20 °C until analysis; hemolyzed samples were excluded.



Figure 1. Venous blood sample collection from a study participant.

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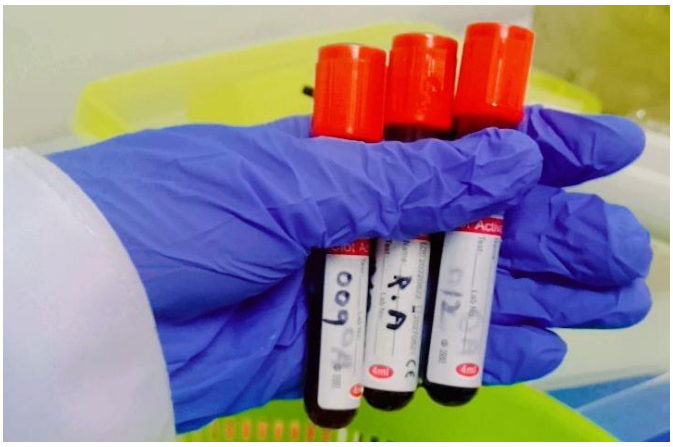


Figure 2. Labeled serum collection tubes containing clotting activator.

Alkaline phosphatase activity measurement

Serum ALP activity was measured using an IFCC-approved kinetic assay kit based on the DGKC (German Society for Clinical Chemistry) method. In this assay, ALP catalyzes the hydrolysis of p-nitrophenylphosphate (pNPP) at alkaline pH, releasing p-nitrophenol and inorganic phosphate; Mg^{2+} ions enhance enzymatic activity. The reaction was monitored as an increase in absorbance at 405 nm, which is directly proportional to serum ALP activity. The working reagent was prepared by mixing four parts Reagent 1 (1 mmol/L diethanolamine buffer, pH 9.80, with 0.6 mmol/L magnesium chloride) with one part Reagent 2 (10 mmol/L pNPP solution). Approximately 20 µL of serum was added to 1000 µL of working reagent, and absorbance was recorded at 405 nm at 37 °C over 3 minutes using a UV-1800 Shimadzu spectrophotometer. The average absorbance change per minute was multiplied by a factor of 3250 to yield ALP activity in U/L.

Malondialdehyde (MDA) estimation

Serum MDA was quantified using the thiobarbituric acid reactive substances (TBARS) method. Samples and standards were treated with 10% trichloroacetic acid (TCA, 0.5 mL), 8.1% sodium dodecyl sulphate (SDS, 0.2 mL), and 0.8% thiobarbituric acid (TBA, 1.5 mL), then heated in a boiling water bath for 1 hour and subsequently cooled on ice. Three milliliters of n-butanol was added, and the mixture was vortexed and centrifuged at 4000 rpm for 10 minutes. The resulting pink organic layer was separated, and absorbance was read at 532 nm.

Working standards of 1,1,3,3-tetraethoxypropane (a stable MDA precursor) were prepared at 10, 20, 30, and 40 nM concentrations, alongside test, control, and blank samples processed under identical conditions (Table below shows the assay volumes used for each reagent across standards, test, control, and blank). MDA concentration was calculated using the formula:

Concentration of MDA (nM/mL) = (Absorbance of test × Concentration of standard × 1000) / (Absorbance of standard × Volume of sample)

Statistical analysis

Data were expressed as mean ± standard deviation (SD) for continuous variables and as number (n) and percentage (%) for categorical variables. Mean ALP and MDA levels were compared between the patient (OA/RA) and control groups.

Results

Demographic and clinical characteristics

Of the 41 patients enrolled, 35 (85.4%) had OA and 6 (14.6%) had RA. Most patients (53.7%) were aged 20–40 years, 31.7% were aged 41–55 years, and 14.6% were aged 56–70 years. Diagnosis was most commonly confirmed by blood tests (36.6%), followed by X-ray (22.0%), physical examination (19.5%), a combination of all diagnostic modalities (12.2%), and MRI (9.8%) alone. A majority of patients (63.4%) had a prior

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history of OA or RA, and most were managed with medication (90.2%) rather than surgery (9.8%) (Table 1).

Table 1. Demographic and clinical characteristics of the study population (n = 41).
Serum ALP activity

Variable	n	%	
Type of arthritis			
Osteoarthritis (OA)	35	85.36	
Rheumatoid arthritis (RA)	6	14.63	
Age (years)			
20–40	22	53.65	
41–55	13	31.70	
56–70	6	14.63	
Diagnostic method			
Physical examination	8	19.51	
Blood test	15	36.58	
X-Ray	9	21.95	
MRI	4	9.75	
Combination of all methods	5	12.19	
History of OA/RA			
Yes	26	63.41	
No	15	36.58	
Treatment			
Medication	37	90.24	
Surgery	4	9.75	

Mean serum ALP activity was considerably higher in OA/RA patients (109.83 ± 246.88 U/L) than in healthy controls (60.33 ± 36.06 U/L) (Figure 3), consistent with increased osteoblastic and bone-remodeling activity in arthritis.

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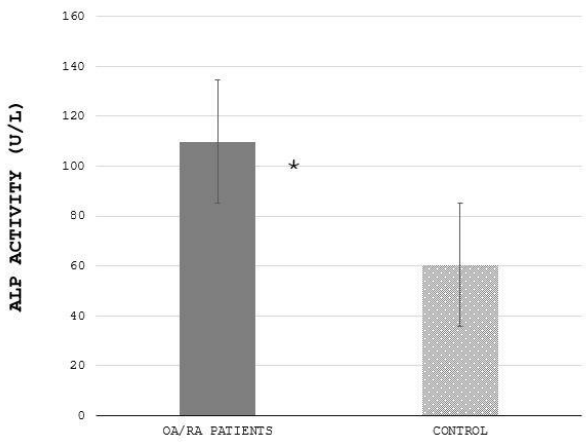


Figure 3. Serum alkaline phosphatase (ALP) activity in OA/RA patients versus healthy controls (mean ± SD; *p < 0.05).

Serum MDA levels

Mean serum MDA levels were markedly higher in OA/RA patients (230.14 ± 163.89 nM/mL) than in controls (43.54 ± 28.53 nM/mL) (Figure 4), indicating substantially elevated oxidative stress in patients with arthritis.

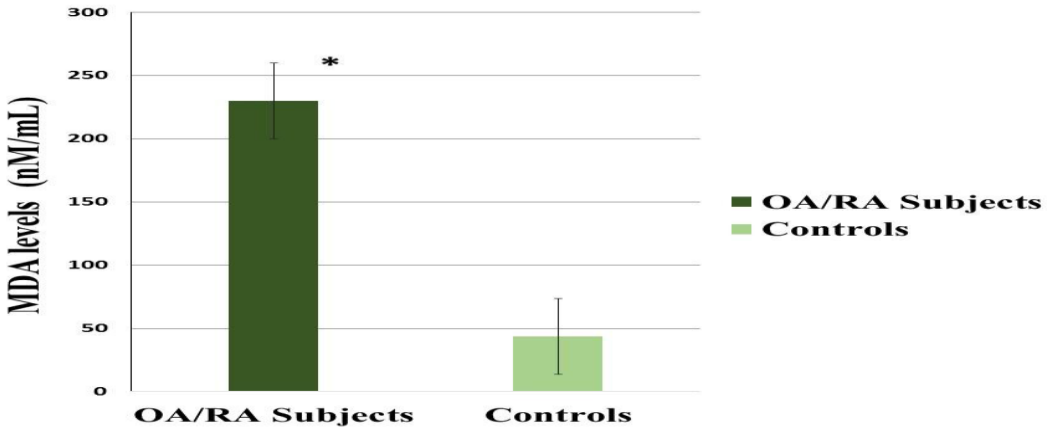


Figure 4. Serum malondialdehyde (MDA) levels in OA/RA patients versus healthy controls (mean ± SD; *p < 0.05).

Discussion

This study demonstrates that both serum ALP activity and MDA levels are markedly elevated in patients with OA and RA compared with healthy controls, supporting the hypothesis that increased bone turnover and heightened oxidative stress are shared features of these arthritic conditions.

ALP is a multifunctional enzyme expressed in the liver, bone, intestine, and placenta, where it catalyzes the dephosphorylation of a range of substrates and plays a key role in phosphate metabolism, bone mineralization, and remodeling (7–15). In the gut, intestinal ALP additionally contributes to mucosal defense by neutralizing bacterial lipopolysaccharide and regulating lipid absorption (16–18). Because ALP is expressed on the osteoblast plasma membrane, elevated serum levels in OA and RA patients most plausibly reflect

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increased osteoblastic activity secondary to subchondral bone remodeling, periarticular inflammation, or compensatory bone formation, although muscle atrophy, medication use, and disease-related inflammation may also contribute (39, 40). Clinically, ALP has established utility in evaluating hepatobiliary and skeletal disease and, more recently, has been explored as a biomarker of periodontal and gut inflammation and as a modifier of drug and nanocarrier pharmacokinetics (16–18, 45–48).

MDA, a terminal product of polyunsaturated fatty acid peroxidation, is one of the most widely used biomarkers of oxidative stress and has been applied across numerous disease contexts, including cancer, cardiovascular disease, and inflammatory arthropathies (54). The marked elevation of serum MDA observed in our OA/RA cohort is consistent with previous reports linking oxidative stress to synovial inflammation, cartilage degradation, and impaired antioxidant defense in arthritis (52, 53). Chronic inflammation in both OA and RA can amplify ROS production while simultaneously compromising enzymatic and non-enzymatic antioxidant capacity, creating a self-perpetuating cycle of oxidative damage and joint tissue injury (41–44).

Bone turnover markers, including ALP, have previously been proposed as tools for predicting postmenopausal bone loss, fracture risk, and response to antiresorptive therapy in osteoporosis, although consensus on their optimal clinical application remains limited (55). Similarly, combined assessment of ALP and MDA may offer complementary insight into disease activity in arthritis—capturing both the skeletal remodeling and oxidative components of disease pathophysiology—but barriers including marker standardization, cost, and the absence of clear clinical guidelines currently limit their routine adoption.

This study has several limitations. The sample size, particularly for the RA group (n = 6), was small and restricted to female patients, limiting the generalizability of the findings and precluding meaningful subgroup or multivariate analysis. The cross-sectional design does not permit assessment of causality or disease trajectory, and confounding factors such as disease duration, severity, and medication regimen were not stratified in the analysis. Larger, longitudinal, and sex-balanced studies incorporating multivariate adjustment are warranted to validate ALP and MDA as clinically actionable biomarkers in arthritis.

Conclusion

Serum ALP and MDA levels were significantly elevated in patients with osteoarthritis and rheumatoid arthritis compared with healthy controls, reflecting increased bone turnover and oxidative stress associated with these conditions. These findings support the potential value of ALP and MDA as complementary, low-cost biochemical markers for assessing disease activity and monitoring treatment response in arthritis. Larger prospective studies are needed to establish their diagnostic and prognostic utility in routine clinical practice.

Conflict of Interest

The authors declare no conflict of interest.

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