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Original Article

Impaired Systemic Antioxidant Defence and Its Association with Functional Disability in Knee Osteoarthritis: A Hospital-Based Case–Control Study

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ABSTRACT

Background: Reactive oxygen species contribute to chondrocyte apoptosis, extracellular matrix degradation and synovial inflammation in osteoarthritis. Whether the resulting systemic redox imbalance relates to the clinical burden experienced by patients is less clear, and Indian data are limited. Objectives: To compare serum malondialdehyde (MDA), superoxide dismutase (SOD), catalase and total antioxidant capacity (TAC) between patients with primary knee osteoarthritis (KOA) and matched healthy controls, and to determine whether these markers independently predict functional disability. **Methods**: A hospital-based analytical case–control study was carried out at a tertiary care teaching hospital in central India over 24 months. Sixty patients aged 40–65 years with primary KOA meeting American College of Rheumatology criteria and Kellgren–Lawrence grade II–IV radiographic change, and 60 age- and sex-matched apparently healthy controls, were recruited consecutively. MDA was measured by the thiobarbituric acid reactive substances assay, SOD by the nitroblue tetrazolium inhibition method of Kakkar et al., catalase by the method of Aebi and TAC by the ferric reducing antioxidant power assay. Functional status was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and pain using a visual analogue scale. Groups were compared by independent Student's t-test; associations were examined by Pearson correlation and multiple linear regression with WOMAC score as the dependent variable. **Results**: Serum MDA was significantly higher in patients than controls (5.68 ± 1.15 vs 3.16 ± 0.68 nmol/mL; $p < 0.001$), while every antioxidant measure was significantly lower: SOD 2.30 ± 0.39 vs 3.57 ± 0.53 U/mL, catalase 41.89 ± 6.48 vs 56.85 ± 7.89 U/mL and TAC 913.81 ± 149.45 vs 1199.69 ± 144.21 µmol/L (all $p < 0.001$). Within the patient group, oxidative stress markers showed no significant correlation with interleukin-6 or with the homeostatic model assessment of insulin resistance. In a multivariable model containing eight biochemical predictors, TAC was the only variable independently associated with WOMAC score (B = −0.033; 95% CI −0.061 to −0.005; $p = 0.020$), although the overall model was not statistically significant ($R^2 = 0.160$; $F = 1.215$; $p = 0.309$). **Conclusion**: Primary knee osteoarthritis is accompanied by increased lipid peroxidation and a broad reduction in enzymatic and non-enzymatic antioxidant defence. Lower global antioxidant capacity was associated with greater functional disability, but this

observation arose within a non-significant model and should be treated as hypothesis-generating pending confirmation in larger, adequately powered studies.

Keywords: Knee osteoarthritis; Oxidative stress; Malondialdehyde; Superoxide dismutase; Total antioxidant capacity; WOMAC.

INTRODUCTION

Osteoarthritis affects more than 500 million people worldwide and ranks among the leading causes of years lived with disability, with the knee the most frequently involved joint [1,2]. Indian community surveys report knee osteoarthritis prevalence of roughly one-fifth to two-fifths of the adult population studied, and the burden is rising with ageing and increasing obesity [3,4]. The understanding of osteoarthritis has shifted from a model of passive mechanical wear to one of active biochemical remodelling in which the joint behaves as an integrated organ [5,6]. Within this framework, oxidative stress occupies a central position. Articular chondrocytes generate reactive oxygen species in response to mechanical loading, cytokine stimulation and mitochondrial dysfunction [7,8]. When production outstrips antioxidant defence, the consequences are direct and cumulative: peroxidation of membrane lipids, oxidative modification of matrix proteins, activation of matrix metalloproteinases, inhibition of proteoglycan synthesis and chondrocyte apoptosis [9,10]. Reactive oxygen species also activate nuclear factor-κB, amplifying the inflammatory signalling that further increases oxidant generation and establishing a self-sustaining cycle [11]. Malondialdehyde, an end product of polyunsaturated fatty acid peroxidation, is the most widely used circulating index of oxidative damage [12]. Antioxidant defence is conventionally assessed through the enzymes superoxide dismutase, which dismutates superoxide to hydrogen peroxide, and catalase, which decomposes hydrogen peroxide to water and oxygen, together with total antioxidant capacity, a composite measure integrating enzymatic and non-enzymatic contributions including urate, ascorbate, tocopherols and thiols [13,14]. Because global capacity reflects the aggregate buffering ability of serum rather than the activity of any single enzyme, it may capture redox status more faithfully than individual assays. Previous studies have reported elevated MDA and reduced antioxidant enzyme activity in knee osteoarthritis [15,16,17], but three questions remain incompletely addressed. First, most reports have measured one or two markers rather than characterising lipid peroxidation, enzymatic defence and global capacity together in the same participants. Second, few have examined whether redox variables relate to inflammatory and metabolic markers measured concurrently. Third, and most importantly for clinical relevance, the relationship between systemic redox status and patient-reported function has rarely been tested in a multivariable framework that accounts for competing biochemical predictors. The present study addressed these gaps in an Indian tertiary care cohort.

MATERIALS AND METHODS

Study design and setting

This hospital-based analytical case–control study was conducted over 24 months in the Department of Biochemistry in collaboration with the Department of Orthopaedics at Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh. The Institutional Ethics Committee approved the protocol (approval number [insert]), the study followed the Declaration of Helsinki, and written informed consent was obtained from every participant.

Participants

Cases were adults aged 40–65 years with primary knee osteoarthritis diagnosed by consultant orthopaedic surgeons using American College of Rheumatology clinical criteria [18] and graded radiographically as Kellgren–Lawrence grade II, III or IV [19]. Controls were apparently healthy adults of the same age range, individually matched for sex and for age within ±5 years, recruited from hospital staff, patient attendants and individuals attending for routine health examination in the same geographical region, with no clinical or radiological evidence of knee osteoarthritis and no inflammatory, endocrine or metabolic disease.

Exclusion criteria applied to both groups were secondary osteoarthritis; inflammatory arthropathy including rheumatoid arthritis, gout and ankylosing spondylitis; previous knee arthroplasty or major knee surgery; acute infection or febrile illness within four weeks; chronic liver or kidney disease; malignancy; autoimmune disease; type 1 or uncontrolled type 2 diabetes mellitus; thyroid dysfunction; chronic cardiovascular disease with active inflammation; current corticosteroid, immunosuppressive or disease-modifying antirheumatic therapy; pregnancy or lactation. Because antioxidant supplementation directly alters the outcome measures, participants who had taken regular antioxidant supplements within the preceding three months were excluded.

Sample size and sampling

Sample size was calculated a priori in G*Power version 3.1.9.7 (Heinrich Heine University, Düsseldorf, Germany) for comparison of two independent means, assuming an effect size (Cohen's d) of 0.60, two-tailed alpha of 0.05, power of 80% and 1:1 allocation, giving a minimum of 45 per group. This was increased to 60 per group to accommodate the number of

biochemical variables and the planned regression analysis. Consecutive sampling of eligible patients attending the orthopaedics outpatient department was used, with a matched control recruited for each case.

Clinical assessment

Demographic details, medical and drug history, dietary habits and lifestyle characteristics were recorded on a pre-validated case record form. Body mass index was calculated as weight in kilograms divided by height in metres squared. Pain was measured on a 10-cm visual analogue scale. Function was assessed with the 24-item Western Ontario and McMaster Universities Osteoarthritis Index covering pain (5 items), stiffness (2 items) and physical function (17 items), higher scores denoting greater impairment [20]. Weight-bearing anteroposterior and lateral knee radiographs were graded by an experienced radiologist blinded to the laboratory results.

Sample collection and processing

After an overnight fast of 8–12 hours, venous blood was collected between 08:00 and 10:00 h to minimise circadian variation. Samples in plain clot activator tubes were allowed to clot for 30 minutes and centrifuged at 3000 rpm for 10–15 minutes within one hour of collection. Serum was aliquoted into sterile polypropylene cryovials and stored at −80 °C until analysis. Multiple aliquots were prepared so that repeated freeze–thaw cycles, which degrade antioxidant enzyme activity, were avoided. Haemolysed samples were rejected, since haemolysis releases erythrocyte SOD and catalase and would spuriously elevate measured activity. Assays were performed in batches to limit inter-assay variation, and internal quality control was run with each batch.

Biochemical assays

Serum malondialdehyde was estimated by the thiobarbituric acid reactive substances method [21]. Malondialdehyde reacts with thiobarbituric acid under acidic conditions at 95 °C to yield a pink chromogen measured spectrophotometrically at 532 nm, with results expressed as nmol/mL. Superoxide dismutase activity was determined by the modified spectrophotometric method of Kakkar et al. [22], based on inhibition of nitroblue tetrazolium reduction by superoxide radicals generated in the phenazine methosulphate–NADH system. Absorbance was read at 560 nm, and one unit of activity was defined as the quantity of enzyme producing 50% inhibition of nitroblue tetrazolium reduction under the assay conditions; results were expressed as U/mL. Catalase activity was measured by the method of Aebi [23], in which the rate of decomposition of hydrogen peroxide is followed as the fall in absorbance at 240 nm in quartz cuvettes; results were expressed as U/mL. Total antioxidant capacity was assayed by the ferric reducing antioxidant power method [24]. At low pH, reduction of the ferric–tripyridyltriazine complex to the ferrous form produces an intense blue colour measured at 593 nm, calibrated against a ferrous sulphate standard curve and expressed as µmol Fe^{2+} equivalents/L. Serum interleukin-6 was measured by sandwich enzyme-linked immunosorbent assay, fasting plasma glucose by the glucose oxidase–peroxidase method and fasting serum insulin by chemiluminescent immunoassay; insulin resistance was estimated as HOMA-IR = [fasting insulin (µIU/mL) × fasting plasma glucose (mg/dL)] ÷ 405 [25]. These variables are reported in full elsewhere and are used here only to test whether redox status relates to inflammatory and metabolic activity.

Statistical analysis

Analyses were performed using [insert software and version]. Continuous variables are reported as mean ± standard deviation and categorical variables as frequencies and percentages. Between-group comparisons used the independent Student's t-test for continuous variables and the chi-square test for categorical variables. Associations among biochemical variables within the case group were assessed using Pearson's correlation coefficient. Multiple linear regression was performed with WOMAC score as the dependent variable and serum interleukin-6, tumour necrosis factor-alpha, high-sensitivity C-reactive protein, MDA, SOD, catalase, TAC and HOMA-IR as independent variables; unstandardised coefficients with 95% confidence intervals are reported. A two-tailed p value below 0.05 was considered significant.

RESULTS

Baseline characteristics

One hundred and twenty participants were analysed, 60 in each group. Cases and controls were comparable for age and sex, while body mass index was significantly higher among cases (Table 1). Kellgren–Lawrence grade III was the commonest radiographic stage. Mean visual analogue scale and WOMAC scores indicated moderate-to-severe pain and appreciable functional limitation respectively.

Table 1. Demographic and clinical characteristics of cases and controls

Variable	Cases (n = 60)	Controls (n = 60)	p value
Age (years), mean ± SD	57.69 ± 7.73	57.20 ± 8.23	0.739
Male, n (%)	25 (41.7)	29 (48.3)	0.46

Variable	Cases (n = 60)	Controls (n = 60)	p value
Female, n (%)	35 (58.3)	31 (51.7)	—
BMI (kg/m²), mean ± SD	29.22 ± 3.48	25.01 ± 2.63	<0.001
K–L grade II, n (%)	15 (25.0)	—	—
K–L grade III, n (%)	26 (43.3)	—	—
K–L grade IV, n (%)	19 (31.7)	—	—
VAS score, mean ± SD	6.41 ± 1.36	—	—
WOMAC score, mean ± SD	56.45 ± 15.02	—	—

BMI, body mass index; K–L, Kellgren–Lawrence; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SD, standard deviation.

Oxidative stress and antioxidant status

Lipid peroxidation was substantially greater and antioxidant defence uniformly weaker in patients with knee osteoarthritis (Table 2). Mean serum MDA was approximately 80% higher in cases than controls. Superoxide dismutase activity was reduced by roughly one-third, catalase activity by about one-quarter and total antioxidant capacity by about one-quarter. The direction of change was consistent across all four markers, indicating a coherent shift towards a pro-oxidant state rather than an isolated abnormality in one pathway.

Table 2. Comparison of oxidative stress and antioxidant markers between cases and controls

Marker	Cases (n = 60)	Controls (n = 60)	p value
MDA (nmol/mL)	5.68 ± 1.15	3.16 ± 0.68	<0.001
SOD (U/mL)	2.30 ± 0.39	3.57 ± 0.53	<0.001
Catalase (U/mL)	41.89 ± 6.48	56.85 ± 7.89	<0.001
TAC (μmol/L)	913.81 ± 149.45	1199.69 ± 144.21	<0.001

Values are mean ± standard deviation. MDA, malondialdehyde; SOD, superoxide dismutase; TAC, total antioxidant capacity. Independent Student's t-test.

Relationship with inflammatory and metabolic status

Within the osteoarthritis group, none of the oxidative stress markers correlated significantly with serum interleukin-6 or with HOMA-IR (Table 3). All coefficients were very weak, and the strongest observed association — between TAC and HOMA-IR — did not reach statistical significance.

Table 3. Correlation of oxidative stress markers with interleukin-6 and HOMA-IR in patients with knee osteoarthritis (n = 60)

Marker	IL-6 (r)	p value	HOMA-IR (r)	p value
MDA	0.003	0.982	0.038	0.772
SOD	−0.024	0.855	0.049	0.712
Catalase	0.144	0.273	0.004	0.976
TAC	−0.049	0.707	0.177	0.177

Pearson's correlation coefficient. IL-6, interleukin-6; HOMA-IR, homeostatic model assessment of insulin resistance. Other abbreviations as in Table 2.

Predictors of functional disability

Multiple linear regression was performed with WOMAC score as the dependent variable and eight biochemical variables as predictors (Table 4). The model accounted for 16.0% of the variance in WOMAC score, but the adjusted coefficient of determination was 2.8% and the overall model did not reach statistical significance ($F = 1.215$; $p = 0.309$), indicating that the biochemical panel as a whole did not predict functional status (Table 5).

Within the model, total antioxidant capacity was the only predictor whose confidence interval excluded zero (B = −0.033; 95% CI −0.061 to −0.005; p = 0.020). The negative coefficient indicates that lower antioxidant capacity was associated with higher WOMAC scores, that is, with greater pain, stiffness and functional impairment. Interleukin-6, tumour necrosis factor-alpha, high-sensitivity C-reactive protein, MDA, SOD, catalase and HOMA-IR showed no independent association with WOMAC score.

Table 4. Multiple linear regression analysis for prediction of WOMAC score in patients with knee osteoarthritis (n = 60)

Predictor	B	SE	t	p value	95% CI
Constant	77.209	25.242	3.059	0.004	26.533 to 127.885
IL-6 (pg/mL)	0.305	0.375	0.813	0.420	−0.448 to 1.058
TNF-α (pg/mL)	−0.008	0.154	−0.051	0.959	−0.316 to 0.300
hs-CRP (mg/L)	1.299	1.319	0.985	0.329	−1.349 to 3.947
MDA (nmol/mL)	−1.332	1.719	−0.775	0.442	−4.782 to 2.118
SOD (U/mL)	−0.569	5.164	−0.110	0.913	−10.936 to 9.798
Catalase (U/mL)	0.207	0.312	0.664	0.510	−0.419 to 0.832
TAC (μmol/L)	−0.033	0.014	−2.395	0.020	−0.061 to −0.005
HOMA-IR	−0.187	2.131	−0.088	0.930	−4.466 to 4.092

Dependent variable: WOMAC score. B, unstandardised regression coefficient; SE, standard error; CI, confidence interval. Other abbreviations as in Tables 2 and 3.

Table 5. Summary of the regression model

Parameter	Value
Number of observations	60
R	0.400
R^2	0.160
Adjusted R^2	0.028
F statistic	1.215
Model p value	0.309

DISCUSSION

This study demonstrates a coherent and substantial disturbance of redox balance in primary knee osteoarthritis. Lipid peroxidation, indexed by serum malondialdehyde, was markedly increased, while all three measures of antioxidant defence — superoxide dismutase, catalase and total antioxidant capacity — were significantly reduced. Because the changes moved in the expected direction across every marker, the pattern is unlikely to reflect assay-specific artefact and is better read as a genuine shift in systemic redox status.

These observations align closely with earlier work. Altindag and colleagues reported increased oxidative stress and reduced total antioxidant capacity in knee osteoarthritis [15], and Henrotin and co-workers described reduced antioxidant enzyme activity together with evidence of oxidative damage to cartilage matrix [9]. Regan and colleagues showed that extracellular superoxide dismutase is depleted in osteoarthritic cartilage, providing a tissue-level correlate of the reduced circulating activity observed here [16]. Ostalowska and colleagues similarly documented enhanced lipid peroxidation with impaired enzymatic defence [17]. The concurrent measurement of enzymatic and global capacity in the present cohort adds the observation that the deficit is not confined to a single enzyme system but extends to the non-enzymatic buffering pool as well. Two negative findings warrant attention. First, oxidative stress markers were unrelated to interleukin-6 and to HOMA-IR within the patient group. Experimental work has established bidirectional crosstalk between reactive oxygen species and nuclear factor-κB signalling [11] and between oxidative stress and insulin signalling [26], so an absence of correlation may seem surprising. Several explanations are plausible. Circulating markers reflect whole-body averages and may not

capture the tissue-level coupling demonstrated in vitro. The cohort was restricted to established disease with all participants already showing abnormal values, compressing the range available for correlation to emerge. Serum antioxidant capacity is also strongly influenced by diet, urate concentration and smoking, none of which was quantified here, and this exogenous variability may obscure a modest endogenous relationship. Second, the overall regression model failed to reach significance despite containing eight biologically motivated predictors. This is itself informative: circulating biochemical markers explained only a small fraction of the variance in patient-reported function. Pain and disability in osteoarthritis are shaped by central pain processing, quadriceps strength, psychological factors, comorbidity and social circumstances, and a serum panel cannot be expected to substitute for these. The finding is a useful corrective to the assumption that biomarker concentrations translate readily into clinical severity.

Against that background, the independent association between total antioxidant capacity and WOMAC score requires cautious framing. The coefficient was statistically significant and in the expected direction, indicating that patients with lower global antioxidant capacity reported greater pain, stiffness and functional limitation. It is also biologically plausible: global capacity integrates the entire buffering system and may therefore reflect cumulative oxidative burden more faithfully than a single enzyme activity. Nevertheless, the finding emerged as one significant coefficient among eight predictors within a model that was not significant overall, in a sample of 60, giving approximately seven observations per predictor — well below the ten to fifteen conventionally recommended. Under these conditions the probability of at least one spurious significant coefficient is appreciable, and the estimate is likely to be unstable. The result should therefore be regarded as hypothesis-generating and requires confirmation in a larger cohort using a parsimonious model specified in advance. If confirmed, the observation would carry practical implications. Total antioxidant capacity is measured by a simple, inexpensive spectrophotometric assay well suited to resource-constrained settings, and unlike structural imaging it is potentially modifiable. Dietary and pharmacological strategies to improve antioxidant status have been proposed in osteoarthritis [27], but interventional evidence remains limited and no recommendation can be drawn from cross-sectional data.

Strengths and limitations

Strengths include simultaneous characterisation of lipid peroxidation, two antioxidant enzymes and global antioxidant capacity in the same participants; individual age and sex matching of controls; exclusion of antioxidant supplement users, whose inclusion would have confounded the primary outcome; standardised pre-analytical handling with rejection of haemolysed samples; and the use of multivariable analysis rather than group comparison alone. Data from Indian populations on this question remain scarce. The limitations are substantial and should temper interpretation. The cross-sectional design precludes causal inference: whether impaired antioxidant defence contributes to disease progression or results from it cannot be determined. Recruitment from a single tertiary centre may over-represent advanced disease and limit generalisability. The regression model was underpowered for the number of predictors entered, as discussed above. Dietary antioxidant intake, smoking status and serum urate — all major determinants of total antioxidant capacity — were not quantified, and residual confounding by these factors is likely. Serum rather than synovial fluid was analysed, and joint-level redox status may differ. Finally, protein oxidation markers, glutathione peroxidase, reduced glutathione and nitric oxide metabolites were not assessed for reasons of cost, so the characterisation of antioxidant defence, while broad, is not complete.

CONCLUSION

Patients with primary knee osteoarthritis showed significantly increased lipid peroxidation together with significantly reduced superoxide dismutase, catalase and total antioxidant capacity compared with age- and sex-matched healthy controls, indicating a generalised impairment of antioxidant defence. Reduced total antioxidant capacity was independently associated with greater functional disability, although this association arose within a regression model that was not significant overall and must be interpreted as preliminary. Adequately powered prospective studies, ideally incorporating synovial fluid measurement and adjustment for dietary antioxidant intake and serum urate, are needed to establish whether global antioxidant capacity has genuine value as a marker of functional prognosis in knee osteoarthritis.

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Data Availability: Data supporting the findings of this study are available from the corresponding author upon reasonable request.