

Psychological Stress and Its Influence on Systemic Inflammatory Markers among Adults with Early Osteoarthritis: A Prospective Analytical StudyDrashti Gosai¹, Deep Parmar², Meetkumar Girishbhai Patel³¹MBBS (Intern), Parul Institute of Medical Sciences and Research, Limda (Vadodara), Gujarat, India²MBBS (Intern), GMERS Medical College, Patan, Gujarat, India³Postgraduate Resident, Department of General Medicine, GMERS Medical College, Gandhinagar, Gujarat, India

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Abstract**Background:** Osteoarthritis (OA) is increasingly recognized as a condition influenced by systemic factors, including psychological stress. The relationship between chronic psychological stress and inflammatory processes in early osteoarthritis remains incompletely characterized, despite evidence supporting psychoneuro immunological pathways in chronic diseases.**Methods:** A total of 194 adults with early radiographic osteoarthritis (Kellgren-Lawrence grade I-II) were enrolled. Psychological stress was assessed using the Perceived Stress Scale (PSS-10) and Depression Anxiety Stress Scales (DASS-21). Serum inflammatory markers including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and cortisol were measured at baseline and 6 months. Multiple regression and mediation analyses examined stress-inflammation relationships.**Results:** Mean age was 54.6 ± 7.8 years, with 58.2% females. High psychological stress (PSS-10 ≥ 20) was present in 42.3% of participants. Individuals with high stress demonstrated significantly elevated hs-CRP (3.84 ± 1.92 mg/L vs. 2.16 ± 1.24 mg/L; $p < 0.001$) and IL-6 (5.47 ± 2.38 pg/mL vs. 3.24 ± 1.76 pg/mL; $p < 0.001$) compared to low-stress counterparts. PSS-10 scores correlated positively with hs-CRP ($r = 0.486$, $p < 0.001$), IL-6 ($r = 0.423$, $p < 0.001$), and TNF- α ($r = 0.368$, $p < 0.001$). Baseline stress predicted 6-month inflammatory marker levels ($\beta = 0.324$, $p < 0.001$) independent of disease severity and demographics. Cortisol dysregulation partially mediated the stress-inflammation relationship (indirect effect: $\beta = 0.087$, 95% CI: 0.042-0.156).**Conclusion:** Psychological stress demonstrates significant associations with elevated systemic inflammatory markers in early osteoarthritis, with evidence of prospective influence. These findings support integrating psychological assessment and stress management into comprehensive osteoarthritis care.**Keywords:** Osteoarthritis; Psychological Stress; Inflammation; C-Reactive Protein; Interleukin-6; Cortisol; Psychoneuroimmunology.

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Introduction

Osteoarthritis (OA) affects over 500 million individuals worldwide, representing the most common form of arthritis and a leading contributor to global disability burden [1]. Traditionally conceptualized as a degenerative "wear and tear" condition, contemporary understanding recognizes osteoarthritis as a complex disorder involving mechanical, metabolic, and inflammatory processes [2]. Early-stage osteoarthritis presents a critical window for intervention, as disease-modifying approaches may have greatest efficacy before advanced structural damage occurs.

Low-grade systemic inflammation has emerged as a significant feature of osteoarthritis pathophysiology, with elevated circulating

inflammatory markers observed even in early disease stages [3]. Pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP) have been implicated in cartilage degradation, synovial inflammation, and disease progression [4]. Understanding factors that modulate inflammatory burden may identify novel therapeutic targets and inform comprehensive management approaches.

Psychological stress represents a ubiquitous aspect of modern life with established implications for physical health. Chronic stress activates the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system, producing sustained alterations in neuroendocrine and immune

function [5]. The field of psychoneuroimmunology has elucidated pathways through which psychological factors influence inflammatory processes, with chronic stress associated with elevated inflammatory markers in diverse populations [6].

The relationship between psychological stress and inflammation in osteoarthritis has received increasing attention. Patients with osteoarthritis frequently experience chronic pain, functional limitations, and reduced quality of life, creating potential for sustained psychological distress [7]. Conversely, psychological factors may influence disease expression through inflammatory pathways. Cross-sectional investigations have demonstrated associations between psychological distress and pain severity, functional limitation, and inflammatory markers in osteoarthritis populations [8]. Cortisol, the primary glucocorticoid stress hormone, plays a central role in stress-inflammation interactions. Under acute stress, cortisol exerts anti-inflammatory effects; however, chronic stress may produce HPA axis dysregulation characterized by blunted cortisol reactivity or chronically elevated baseline levels [9]. This dysregulation may result in glucocorticoid receptor desensitization and diminished capacity to regulate inflammatory responses, thereby promoting systemic inflammation.

Despite accumulating evidence supporting stress-inflammation connections, significant research gaps persist regarding this relationship specifically in early osteoarthritis. Most investigations have examined advanced disease or utilized cross-sectional designs limiting causal inference. Prospective studies examining whether psychological stress predicts subsequent inflammatory marker changes in early OA are scarce. Furthermore, examination of potential mediating mechanisms, including cortisol dysregulation, remains limited. Therefore, this prospective analytical study aimed to investigate the influence of psychological stress on systemic inflammatory markers among adults with early-stage osteoarthritis, examine the temporal relationship between stress and inflammation over 6 months, and explore cortisol as a potential mediating mechanism.

Materials and Methods

Study Design and Setting: This prospective analytical study was conducted at the tertiary care Center.

Sample Size Calculation: Sample size was determined using G* Power software version 3.1.9.7. Based on anticipated moderate correlation ($r=0.30$) between stress and inflammatory markers from preliminary data, with $\alpha=0.05$ and power=0.90, a minimum of 112 participants was required. For multiple regression analysis with 10

predictors and medium effect size ($f^2=0.15$), 172 participants were needed. Accounting for 15% anticipated attrition, target enrollment was established at 200 participants.

Participant Selection: Adults presenting for evaluation of joint symptoms were screened for eligibility. Inclusion criteria comprised: (1) age 40-65 years; (2) clinical and radiographic evidence of hip, knee, or hand osteoarthritis according to American College of Rheumatology criteria; (3) Kellgren-Lawrence radiographic grade I or II (early OA); (4) symptom duration 6-36 months; and (5) ability to complete psychological assessments independently.

Exclusion criteria included: (1) Kellgren-Lawrence grade III-IV (advanced OA); (2) inflammatory arthropathies (rheumatoid arthritis, psoriatic arthritis, gout); (3) current psychiatric disorder requiring medication; (4) use of corticosteroids, immunosuppressants, or psychotropic medications; (5) chronic inflammatory conditions (inflammatory bowel disease, autoimmune disorders); (6) acute infection within preceding 4 weeks; (7) malignancy within 5 years; (8) endocrine disorders affecting HPA axis; and (9) body mass index exceeding 40 kg/m².

Assessment Schedule: Comprehensive evaluations were conducted at baseline and 6-month follow-up. Assessments were performed between 8:00-10:00 AM to minimize circadian variation in cortisol and inflammatory markers.

Psychological Stress Assessment

Perceived Stress Scale (PSS-10): This 10-item validated instrument measures the degree to which life situations are appraised as stressful over the preceding month. Responses utilize 5-point Likert scales (0=never to 4=very often), with total scores ranging 0-40. Higher scores indicate greater perceived stress. Scores were categorized as low stress (0-13), moderate stress (14-19), and high stress (≥ 20).

Depression Anxiety Stress Scales (DASS-21): This 21-item self-report instrument comprises three subscales measuring depression, anxiety, and stress over the preceding week. Each subscale contains 7 items scored 0-3, with subscale scores multiplied by 2 for interpretation. The stress subscale (DASS-S) was utilized as a complementary stress measure.

Life Events Checklist: Participants reported significant stressful life events (financial difficulties, bereavement, relationship problems, occupational stress) occurring within the preceding 6 months.

Inflammatory Marker Assessment: Venous blood samples (15 mL) were collected following overnight fasting (minimum 10 hours). Samples were processed within 2 hours, centrifuged at 3000

rpm for 15 minutes at 4°C, and serum aliquoted and stored at -80°C until batch analysis.

High-sensitivity C-reactive protein (hs-CRP): Measured using particle-enhanced immunonephelometry (Siemens BN II System, Germany) with detection limit 0.15 mg/L and intra-assay coefficient of variation <5%.

Interleukin-6 (IL-6): Quantified using high-sensitivity ELISA (R&D Systems Quantikine HS, Minneapolis, USA) with detection limit 0.039 pg/mL.

Tumor necrosis factor-alpha (TNF- α): Measured using ELISA (R&D Systems Quantikine, Minneapolis, USA) with detection limit 0.5 pg/mL.

Serum cortisol: Measured using electrochemiluminescence immunoassay (Roche Cobas e601, Germany). Morning cortisol (8:00-9:00 AM) was assessed.

Clinical Variables: Demographic data including age, sex, education, employment status, and marital status were recorded. Body mass index (BMI), affected joint location, symptom duration, and radiographic severity (Kellgren-Lawrence grade) were documented. Pain was assessed using Visual Analog Scale (VAS, 0-100 mm). Functional status was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Physical activity level was assessed using the International Physical Activity Questionnaire short form.

Statistical Analysis: Statistical analyses were performed using IBM SPSS version 28.0 and PROCESS macro version 4.2 for mediation

analysis. Continuous variables were assessed for normality and expressed as mean \pm standard deviation or median (interquartile range). Inflammatory markers demonstrating skewed distributions were log-transformed for parametric analyses.

Participants were categorized into stress groups (low, moderate, high) based on PSS-10 scores. Between-group comparisons utilized one-way ANOVA with Bonferroni correction and chi-square tests. Pearson or Spearman correlations examined bivariate relationships. Multiple linear regression identified independent predictors of inflammatory markers, adjusting for age, sex, BMI, disease severity, and physical activity. Hierarchical regression examined whether baseline stress predicted 6-month inflammatory markers after controlling for baseline inflammation.

Mediation analysis examined cortisol as a mediator of stress-inflammation relationships using bootstrapping (5000 iterations) with bias-corrected 95% confidence intervals. Significant mediation was indicated when confidence intervals excluded zero. Statistical significance was defined as $p < 0.05$ (two-tailed).

Results

Baseline Characteristics: Of 224 individuals screened, 194 met eligibility criteria and completed baseline assessments. Follow-up retention was 91.2% ($n=177$) at 6 months. Baseline characteristics stratified by stress level are presented in Table 1.

Table 1: Baseline Demographic and Clinical Characteristics by Stress Category

| Variable | Total (n=194) | Low Stress PSS<14 (n=48) | Moderate Stress PSS 14-19 (n=64) | High Stress PSS \geq 20 (n=82) | p-value |
|---------------------------------------|-----------------|--------------------------|----------------------------------|----------------------------------|---------|
| Age (years) | 54.6 \pm 7.8 | 55.2 \pm 7.4 | 54.8 \pm 8.1 | 54.1 \pm 7.9 | 0.724 |
| Female, n (%) | 113 (58.2) | 24 (50.0) | 36 (56.3) | 53 (64.6) | 0.218 |
| BMI (kg/m ²) | 28.4 \pm 4.2 | 27.2 \pm 3.8 | 28.1 \pm 4.0 | 29.4 \pm 4.4 | 0.012 |
| Education \geq college, n (%) | 98 (50.5) | 28 (58.3) | 34 (53.1) | 36 (43.9) | 0.242 |
| Employed, n (%) | 142 (73.2) | 38 (79.2) | 48 (75.0) | 56 (68.3) | 0.384 |
| Married/partnered, n (%) | 134 (69.1) | 38 (79.2) | 46 (71.9) | 50 (61.0) | 0.082 |
| OA Characteristics | | | | | |
| K-L grade I, n (%) | 86 (44.3) | 24 (50.0) | 30 (46.9) | 32 (39.0) | 0.412 |
| K-L grade II, n (%) | 108 (55.7) | 24 (50.0) | 34 (53.1) | 50 (61.0) | |
| Symptom duration (months) | 18.4 \pm 8.6 | 16.8 \pm 7.8 | 17.6 \pm 8.2 | 19.8 \pm 9.2 | 0.124 |
| VAS pain (mm) | 46.8 \pm 18.4 | 38.4 \pm 16.2 | 44.6 \pm 17.8 | 52.8 \pm 18.2 | <0.001 |
| WOMAC total | 42.6 \pm 18.2 | 34.2 \pm 14.8 | 40.8 \pm 16.4 | 48.6 \pm 19.4 | <0.001 |
| Psychological Measures | | | | | |
| PSS-10 score | 18.4 \pm 6.8 | 9.6 \pm 2.8 | 16.2 \pm 1.6 | 25.4 \pm 4.2 | <0.001 |
| DASS-21 Stress | 14.6 \pm 8.4 | 6.4 \pm 4.2 | 12.8 \pm 5.6 | 20.8 \pm 7.8 | <0.001 |
| DASS-21 Depression | 8.4 \pm 6.8 | 4.2 \pm 3.6 | 6.8 \pm 5.2 | 12.4 \pm 7.4 | <0.001 |
| DASS-21 Anxiety | 7.2 \pm 5.6 | 3.8 \pm 3.2 | 6.4 \pm 4.8 | 10.2 \pm 6.2 | <0.001 |
| Stressful life events \geq 2, n (%) | 78 (40.2) | 10 (20.8) | 22 (34.4) | 46 (56.1) | <0.001 |

Data presented as mean \pm SD or n (%). BMI: body mass index; K-L: Kellgren-Lawrence; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PSS: Perceived Stress Scale; DASS: Depression Anxiety Stress Scales.

High psychological stress (PSS-10 ≥ 20) was present in 42.3% of participants.

Individuals with high stress demonstrated significantly higher BMI ($p=0.012$), greater pain intensity ($p<0.001$), worse functional status ($p<0.001$), and more frequent stressful life events ($p<0.001$).

Inflammatory Markers and Cortisol by Stress Category: Inflammatory marker concentrations stratified by stress category are presented in Table 2.

Significant differences were observed across stress groups for all inflammatory markers.

Table 2: Inflammatory Markers and Cortisol Concentrations by Stress Category

| Biomarker | Low Stress (n=48) | Moderate Stress (n=64) | High Stress (n=82) | p-value | Post-hoc |
|--------------------------------|-------------------|------------------------|--------------------|---------|----------|
| Baseline | | | | | |
| hs-CRP (mg/L) | 2.16 \pm 1.24 | 2.84 \pm 1.56 | 3.84 \pm 1.92 | <0.001 | L<M<H |
| IL-6 (pg/mL) | 3.24 \pm 1.76 | 4.12 \pm 2.04 | 5.47 \pm 2.38 | <0.001 | L<M<H |
| TNF- α (pg/mL) | 4.86 \pm 2.12 | 5.68 \pm 2.34 | 6.84 \pm 2.68 | <0.001 | L<H |
| Morning cortisol (μ g/dL) | 14.2 \pm 4.6 | 16.8 \pm 5.2 | 19.4 \pm 6.8 | <0.001 | L<M<H |
| 6-Month Follow-up | | | | | |
| hs-CRP (mg/L) | 2.24 \pm 1.32 | 3.12 \pm 1.68 | 4.26 \pm 2.14 | <0.001 | L<M<H |
| IL-6 (pg/mL) | 3.38 \pm 1.84 | 4.48 \pm 2.16 | 6.12 \pm 2.64 | <0.001 | L<M<H |
| TNF- α (pg/mL) | 5.02 \pm 2.24 | 5.94 \pm 2.48 | 7.28 \pm 2.86 | <0.001 | L<H |
| Morning cortisol (μ g/dL) | 14.6 \pm 4.8 | 17.4 \pm 5.6 | 20.2 \pm 7.2 | <0.001 | L<M<H |
| Change Scores | | | | | |
| Δ hs-CRP (mg/L) | 0.08 \pm 0.64 | 0.28 \pm 0.78 | 0.42 \pm 0.94 | 0.046 | L<H |
| Δ IL-6 (pg/mL) | 0.14 \pm 0.72 | 0.36 \pm 0.86 | 0.65 \pm 1.12 | 0.008 | L<H |
| Δ TNF- α (pg/mL) | 0.16 \pm 0.68 | 0.26 \pm 0.82 | 0.44 \pm 0.98 | 0.142 | NS |

Data presented as mean \pm SD. Post-hoc: L=low stress, M=moderate stress, H=high stress; Bonferroni correction applied. NS: not significant.

Participants with high stress demonstrated significantly elevated hs-CRP (3.84 \pm 1.92 mg/L vs. 2.16 \pm 1.24 mg/L; $p<0.001$) and IL-6 (5.47 \pm 2.38 pg/mL vs. 3.24 \pm 1.76 pg/mL; $p<0.001$) compared to low-stress individuals.

Morning cortisol was significantly higher in the high-stress group (19.4 \pm 6.8 μ g/dL vs. 14.2 \pm 4.6 μ g/dL; $p<0.001$). Change scores demonstrated

greater inflammatory marker increases in high-stress participants over 6 months.

Correlation and Regression Analyses: Correlation analyses revealed significant positive associations between PSS-10 scores and inflammatory markers (Table 3). PSS-10 correlated with hs-CRP ($r=0.486$, $p<0.001$), IL-6 ($r=0.423$, $p<0.001$), TNF- α ($r=0.368$, $p<0.001$), and morning cortisol ($r=0.412$, $p<0.001$).

Table 3: Correlation Matrix between Psychological Stress Measures and Inflammatory Markers

| Variable | PSS-10 | DASS-S | hs-CRP | IL-6 | TNF- α | Cortisol |
|---------------|----------|----------|----------|----------|---------------|----------|
| PSS-10 | — | | | | | |
| DASS-S | 0.724*** | — | | | | |
| hs-CRP | 0.486*** | 0.418*** | — | | | |
| IL-6 | 0.423*** | 0.384*** | 0.612*** | — | | |
| TNF- α | 0.368*** | 0.326*** | 0.524*** | 0.586*** | — | |
| Cortisol | 0.412*** | 0.378*** | 0.342*** | 0.298*** | 0.264*** | — |
| VAS pain | 0.524*** | 0.468*** | 0.386*** | 0.342*** | 0.312*** | 0.286*** |
| WOMAC | 0.498*** | 0.442*** | 0.364*** | 0.328*** | 0.296*** | 0.268*** |

*** $p<0.001$. PSS: Perceived Stress Scale; DASS-S: DASS-21 Stress subscale; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; TNF- α : tumor necrosis factor-alpha.

Multiple regression analysis for baseline hs-CRP identified PSS-10 ($\beta=0.362$, $p<0.001$), BMI ($\beta=0.248$, $p<0.001$), and female sex ($\beta=0.142$, $p=0.038$) as significant independent predictors (adjusted $R^2=0.324$). Hierarchical regression demonstrated that baseline PSS-10 predicted 6-month hs-CRP ($\beta=0.298$, $p<0.001$) after controlling for baseline hs-CRP, age, sex, BMI, and disease severity ($\Delta R^2=0.067$, $p<0.001$).

Mediation analysis revealed that morning cortisol partially mediated the relationship between perceived stress and hs-CRP. The total effect of PSS-10 on hs-CRP was significant ($c=0.412$, $p<0.001$). The indirect effect through cortisol was significant ($ab=0.087$, 95% CI: 0.042-0.156), while the direct effect remained significant ($c'=0.325$,

$p < 0.001$), indicating partial mediation accounting for 21.1% of the total effect.

Discussion

This prospective analytical study demonstrates significant associations between psychological stress and systemic inflammatory markers in adults with early osteoarthritis. Our findings reveal that elevated perceived stress is associated with increased concentrations of hs-CRP, IL-6, and TNF- α at baseline, and that baseline stress predicts inflammatory marker levels at 6-month follow-up independent of disease severity. Furthermore, cortisol dysregulation partially mediates the stress-inflammation relationship, supporting hypothalamic-pituitary-adrenal axis involvement.

The prevalence of high psychological stress (42.3%) in our early OA cohort underscores the substantial psychological burden associated with this condition even in its initial stages. Prior investigations have documented elevated rates of psychological distress in osteoarthritis populations, though most have focused on advanced disease [10]. The recognition that significant stress is present early in the disease course has implications for timely intervention.

Our observation of positive correlations between perceived stress and inflammatory markers aligns with broader psychoneuroimmunology literature. Chronic psychological stress has been consistently associated with elevated inflammatory markers across diverse populations and health conditions [11]. The magnitude of correlations observed ($r = 0.37-0.49$) suggests clinically meaningful relationships that warrant intervention consideration.

The prospective finding that baseline stress predicts subsequent inflammatory marker levels extends cross-sectional observations and provides stronger evidence for temporal relationships. Similar prospective associations have been reported in cardiovascular disease populations [12]. In the context of early osteoarthritis, this finding suggests that stress may contribute to inflammatory burden over time, potentially influencing disease trajectory. Inflammation has been implicated in osteoarthritis progression, cartilage degradation, and symptom severity [13].

Cortisol emerged as a partial mediator of stress-inflammation relationships, accounting for approximately 21% of the total effect. This finding supports theoretical models positing that chronic stress produces HPA axis dysregulation, leading to altered cortisol patterns and diminished capacity to regulate inflammation [14]. The elevated morning cortisol observed in high-stress participants may reflect chronic HPA activation. Prolonged cortisol elevation can produce glucocorticoid receptor

desensitization, paradoxically permitting unchecked inflammatory responses [15].

The clinical implications of these findings are multifaceted. First, psychological stress assessment should be incorporated into comprehensive evaluation of early osteoarthritis patients. Validated instruments such as the PSS-10 are brief and readily implementable in clinical settings. Second, patients demonstrating elevated stress may benefit from psychological interventions. Stress management techniques, cognitive-behavioral approaches, and mindfulness-based interventions have demonstrated efficacy in reducing psychological distress and inflammatory markers in chronic disease populations [16].

The relationship between stress and pain observed in our cohort warrants consideration. Psychological stress may amplify pain perception through central sensitization mechanisms and enhanced inflammatory signaling [17]. Conversely, chronic pain represents a significant stressor contributing to psychological distress. Addressing both domains simultaneously through integrated biopsychosocial approaches may produce synergistic benefits.

Our findings contribute to the evolving understanding of osteoarthritis as a systemic condition influenced by biological, psychological, and social factors. The biopsychosocial model of chronic pain emphasizes the interconnection of these domains, and psychological factors have been increasingly recognized in osteoarthritis guidelines [18]. Inflammatory pathways may represent one mechanism linking psychological factors to disease expression. Several limitations merit acknowledgment. First, despite the prospective design, observational methodology precludes definitive causal conclusions; randomized trials of stress-reduction interventions would provide stronger evidence. Second, single morning cortisol measurements incompletely characterize HPA axis function; diurnal cortisol patterns or cortisol reactivity measures would enhance understanding. Third, the 6-month follow-up period may be insufficient to detect longer-term relationships. Finally, participants with diagnosed psychiatric conditions requiring medication were excluded, potentially limiting generalizability.

Conclusion

This prospective analytical study demonstrates significant associations between psychological stress and elevated systemic inflammatory markers among adults with early-stage osteoarthritis. High perceived stress is associated with increased concentrations of C-reactive protein, interleukin-6, and tumor necrosis factor-alpha, with baseline stress predicting inflammatory marker levels at 6-month follow-up. Cortisol dysregulation partially

mediates these relationships, supporting hypothalamic-pituitary-adrenal axis involvement in stress-inflammation pathways. These findings highlight the importance of psychological assessment in early osteoarthritis and suggest that stress management interventions may have potential to modulate inflammatory burden. Integrating psychological care into comprehensive osteoarthritis management represents a promising avenue for improving outcomes through addressing the interconnection between mind and body in this prevalent condition. Future intervention studies should examine whether stress reduction translates to improved inflammatory profiles and clinical outcomes in osteoarthritis populations.

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