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ASSOCIATION OF OXIDATIVE STRESS MARKERS AND PRO-INFLAMMATORY CYTOKINES IN PATIENTS WITH CHRONIC RHINOSINUSITIS WITH AND WITHOUT NASAL POLYPS

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Abstract

Objective: To evaluate the association between oxidative stress markers and pro-inflammatory cytokines in patients with chronic rhinosinusitis (CRS) with and without nasal polyps. **Methodology:** This comparative cross-sectional study was conducted at a tertiary care hospital in Lahore, Pakistan, from January 2023 to December 2024. A total of 120 patients diagnosed with CRS were enrolled and divided into two equal groups: CRS without nasal polyps (CRSsNP, n=60) and CRS with nasal polyps (CRSwNP, n=60). Diagnosis was confirmed clinically and by nasal endoscopy and/or computed tomography. Serum levels of malondialdehyde (MDA), total antioxidant capacity (TAC), superoxide dismutase (SOD), catalase, and nitric oxide were measured to assess oxidative stress. Pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and high-sensitivity C-reactive protein (hs-CRP) were quantified using ELISA. Data were analyzed using SPSS, and a p-value <0.05 was considered statistically significant. **Results:** CRSwNP patients demonstrated significantly higher levels of MDA, nitric oxide, IL-6, TNF-α, IL-1β, and hs-CRP compared to CRSsNP patients ($p<0.001$), while antioxidant parameters (TAC, SOD, catalase) were significantly reduced ($p<0.001$). CT severity scores positively correlated with oxidative and inflammatory markers and inversely correlated with antioxidant levels ($p<0.001$). Multivariate analysis identified elevated MDA and IL-6 as independent predictors of nasal polyp formation. **Conclusion:** CRSwNP is characterized by heightened oxidative stress and amplified inflammatory cytokine activity. The significant association between oxidative imbalance and inflammatory mediators suggests their potential role as biomarkers for disease severity and polyp formation in chronic rhinosinusitis.

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INTRODUCTION

Chronic rhinosinusitis (CRS) is a multifactorial inflammatory disorder of the nasal cavity and paranasal sinuses characterized by persistent symptoms lasting more than 12 weeks and objective evidence of mucosal inflammation on nasal endoscopy or computed tomography (CT) imaging.[1] CRS represents a significant global health burden due to its high prevalence, impact on quality of life, and substantial healthcare costs.

The disease is clinically classified into two major phenotypes: chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP).[2] These phenotypes differ not only in endoscopic appearance but also in underlying inflammatory mechanisms, tissue remodeling patterns, recurrence rates, and response to therapy.

Recent advances emphasize the concept of CRS endotypes, which are defined by distinct immunopathological mechanisms rather than clinical features alone.[3] CRSwNP is frequently associated with type 2 inflammation characterized by eosinophilia and elevated cytokines such as interleukin (IL)-4, IL-5, and IL-13, whereas CRSsNP may demonstrate a more heterogeneous inflammatory profile.[2,3]

Central to CRS pathogenesis is dysfunction of the sinonasal epithelial barrier, which normally serves as a protective interface against environmental pathogens and irritants. Epithelial injury results in impaired mucociliary clearance, increased permeability, and activation of innate immune responses, leading to persistent inflammation and tissue remodeling.[4]

Increasing evidence suggests that oxidative stress plays a pivotal role in the initiation and progression of CRS, particularly in patients with nasal polyps.[5] Oxidative stress refers to an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system. Excess ROS can damage cellular lipids, proteins, and DNA, disrupt epithelial integrity, and activate redox-sensitive signaling pathways such as nuclear factor-kappa B (NF-κB), thereby enhancing cytokine production and perpetuating chronic inflammation.[6]

Lipid peroxidation products such as malondialdehyde (MDA) serve as measurable indicators of oxidative damage, while enzymatic antioxidants including superoxide dismutase (SOD) and catalase reflect the body's defense mechanisms against oxidative injury.[5,7] Reduced total antioxidant capacity (TAC) has been reported in CRS patients, further supporting the involvement of oxidative imbalance in disease pathophysiology.

In CRSwNP, oxidative stress may be amplified by infiltrating inflammatory cells, including eosinophils and macrophages, which generate ROS during immune activation.[6] Transcriptomic analyses of nasal mucosa and polyp tissue have demonstrated upregulation of genes associated with oxidative stress and inflammatory pathways, highlighting a close interplay between redox imbalance and immune dysregulation.[7] This oxidant–antioxidant disequilibrium may contribute to mucosal edema, extracellular matrix remodeling, and polyp formation.

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Parallel to oxidative stress, pro-inflammatory cytokines play a crucial role in sustaining sinonasal inflammation. Elevated levels of cytokines such as IL-6, tumor necrosis factor-alpha (TNF-α), and IL-1β have been reported in CRS patients and correlate with disease severity.[8,9] These cytokines promote leukocyte recruitment, vascular permeability, and mucosal hyperplasia, thereby contributing to chronic tissue inflammation.

Systemic elevations of inflammatory mediators further suggest that CRS is not merely a localized disorder but may involve systemic immune activation.[9] Deep immune profiling studies have demonstrated distinct cytokine signatures between CRS phenotypes, reinforcing the importance of biochemical markers in understanding disease heterogeneity.[10]

Although both oxidative stress markers and inflammatory cytokines have independently been implicated in CRS pathogenesis, limited studies have comprehensively evaluated their association within the same patient population, particularly in comparative analyses between CRSwNP and CRSsNP. Understanding the relationship between oxidative damage and cytokine activation may provide insights into phenotype-specific mechanisms and identify potential therapeutic targets.

Therefore, investigating oxidative stress parameters alongside pro-inflammatory cytokines in CRS patients with and without nasal polyps may help clarify the biochemical basis of disease severity and polyp formation.

METHODOLOGY

This comparative cross-sectional study was conducted in the Department of Otorhinolaryngology (ENT), in collaboration with the Department of Biochemistry, at a tertiary care teaching hospital in Lahore, Pakistan, from January 2023 to December 2023.

The study aimed to evaluate and compare oxidative stress markers and pro-inflammatory cytokines in patients diagnosed with chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP).

Patients presenting to the ENT outpatient department or admitted for evaluation and management of chronic rhinosinusitis during the study period were screened for eligibility. A non-probability consecutive sampling technique was employed until the required sample size was achieved. A total of 120 participants were enrolled and divided equally into two groups: 60 patients with CRSsNP and 60 patients with CRSwNP.

The diagnosis of CRS was established based on clinical criteria of persistent symptoms for more than 12 weeks, including nasal obstruction or congestion, nasal discharge or postnasal drip, facial pain or pressure, and/or reduction in sense of smell, along with objective evidence of mucosal inflammation on nasal endoscopy and/or computed tomography (CT) scan of the paranasal sinuses. The presence of visible nasal polyps on endoscopy confirmed CRSwNP.

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Inclusion criteria comprised patients aged 18 to 60 years who fulfilled diagnostic criteria for CRS and provided written informed consent. Patients were excluded if they had acute rhinosinusitis, prior sinonasal surgery, use of systemic corticosteroids or immunosuppressive drugs within the preceding four weeks, chronic systemic inflammatory or autoimmune disorders, malignancy, advanced hepatic or cardiac disease, pregnancy, or any severe metabolic or systemic condition that could influence oxidative stress or inflammatory markers.

All participants underwent a detailed clinical evaluation, including history, general physical examination, and complete ENT examination. Diagnostic nasal endoscopy was performed to classify CRS phenotype, and CT scan findings were reviewed where available. Disease severity was assessed using the Lund–Mackay scoring system.

For biochemical analysis, 5–7 mL of venous blood was collected under aseptic conditions from each participant. Serum was separated by centrifugation and stored at −20°C until analysis.

Oxidative stress parameters assessed included malondialdehyde (MDA) as a marker of lipid peroxidation, total antioxidant capacity (TAC), superoxide dismutase (SOD), catalase, and nitric oxide (measured indirectly through serum nitrite/nitrate levels where applicable).

Pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β), were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to manufacturer instructions. High-sensitivity C-reactive protein (hs-CRP) was also measured as an indicator of systemic inflammation.

The primary outcome measure was the difference in oxidative stress markers and cytokine levels between CRSsNP and CRSwNP groups. Secondary outcomes included correlation of biochemical markers with CT severity score and identification of independent predictors of nasal polyps.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software. Continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed variables were expressed as mean ± standard deviation and compared using the independent sample t-test, whereas non-normally distributed variables were expressed as median (interquartile range) and compared using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and analyzed using the chi-square test or Fisher’s exact test where appropriate.

Correlation between biomarkers and Lund–Mackay score was assessed using Pearson or Spearman correlation analysis. Binary logistic regression was performed to determine independent predictors of nasal polyps, and adjusted odds ratios with 95% confidence intervals were reported. A p-value of less than 0.05 was considered statistically significant.

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Ethical approval was obtained from the Institutional Review Board of the respective tertiary care hospital prior to commencement of the study. Written informed consent was obtained from all participants, and confidentiality was maintained throughout the study by assigning unique identification codes and securely storing study data.

RESULTS

A total of 120 patients were included in the study, comprising 60 patients with chronic rhinosinusitis without nasal polyps (CRSsNP) and 60 patients with chronic rhinosinusitis with nasal polyps (CRSwNP). The two groups were comparable in terms of age and gender distribution ($p>0.05$). However, the duration of symptoms and CT severity (Lund–Mackay) scores were significantly higher in the CRSwNP group ($p<0.001$).

Patients with nasal polyps demonstrated significantly elevated levels of oxidative stress markers, including malondialdehyde (MDA) and nitric oxide, along with significantly reduced antioxidant parameters such as total antioxidant capacity, superoxide dismutase, and catalase ($p<0.001$ for all comparisons). Similarly, pro-inflammatory cytokines including IL-6, TNF-α, IL-1β, and hs-CRP were markedly higher in the CRSwNP group compared to CRSsNP patients ($p<0.001$).

Correlation analysis revealed a significant positive association between inflammatory/oxidative markers and CT severity scores, while antioxidant levels showed an inverse correlation ($p<0.001$). On multivariate regression analysis, elevated MDA and IL-6 levels emerged as independent predictors of nasal polyp formation.

Table 1: Baseline Demographic and Clinical Characteristics

Variable	CRSsNP (n=60)	CRSwNP (n=60)	p-value
Age (years), Mean ± SD	34.6 ± 9.2	36.1 ± 8.8	0.342
Male, n (%)	32 (53.3%)	35 (58.3%)	0.584
Female, n (%)	28 (46.7%)	25 (41.7%)	-
Duration of symptoms (months), Median (IQR)	10 (6–18)	18 (12–30)	0.001
CT Severity Score (Lund-Mackay), Mean ± SD	8.2 ± 2.4	15.6 ± 3.1	<0.001

Table 2: Comparison of Oxidative Stress Markers between Groups

Biomarker	CRSsNP (n=60)	CRSwNP (n=60)	p-value
MDA (nmol/mL), Mean ± SD	3.1 ± 0.8	5.4 ± 1.1	<0.001
Total Antioxidant Capacity (mmol/L), Mean ± SD	1.42 ± 0.26	0.96 ± 0.22	<0.001
Superoxide Dismutase (U/mL), Mean ± SD	2.8 ± 0.7	1.9 ± 0.6	<0.001
Catalase (U/mL), Mean ± SD	48.6 ± 10.2	32.4 ± 8.7	<0.001
Nitric Oxide (µmol/L), Mean ± SD	24.1 ± 5.3	38.7 ± 6.8	<0.001

Table 3: Comparison of Pro-Inflammatory Cytokines Between Groups

Cytokine	CRSsNP (n=60)	CRSwNP (n=60)	p-value
IL-6 (pg/mL), Median (IQR)	6.8 (4.5–9.2)	14.5 (10.8–19.3)	<0.001
TNF-α (pg/mL), Median (IQR)	8.1 (5.6–11.4)	17.2 (13.0–22.6)	<0.001
IL-1β (pg/mL), Median (IQR)	3.2 (2.1–4.8)	7.6 (5.4–10.2)	<0.001
High-sensitivity CRP (mg/L), Median (IQR)	2.4 (1.5–3.8)	5.9 (4.2–8.1)	<0.001

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Table 4: Correlation of Biomarkers with CT Severity Score (All Participants, n=120)

Biomarker	Correlation Coefficient (r)	p-value
MDA	+0.61	<0.001
Total Antioxidant Capacity	-0.54	<0.001
SOD	-0.48	<0.001
IL-6	+0.66	<0.001
TNF-α	+0.63	<0.001
Nitric Oxide	+0.59	<0.001

Table 5: Multivariate Regression Analysis for Predictors of Nasal Polyps

Variable	Adjusted OR	95% CI	p-value
MDA (per unit increase)	2.10	1.45–3.05	<0.001
IL-6 (per pg/mL increase)	1.18	1.09–1.28	<0.001
TNF-α	1.12	1.05–1.20	0.002
Total Antioxidant Capacity	0.41	0.22–0.76	0.004

DISCUSSION

The present study demonstrates a significant association between oxidative stress markers and pro-inflammatory cytokines in patients with chronic rhinosinusitis (CRS), with markedly higher levels observed in those with nasal polyps (CRSwNP) compared to those without polyps (CRSsNP). These findings support the hypothesis that oxidative stress and inflammatory mediators act synergistically in the pathogenesis and progression of CRS, particularly in the polypoid phenotype.

Our results revealed significantly elevated malondialdehyde (MDA) and nitric oxide levels in CRSwNP patients, accompanied by reduced antioxidant defenses including total antioxidant capacity (TAC), superoxide dismutase (SOD), and catalase. This oxidant–antioxidant imbalance is consistent with recent literature suggesting that excessive reactive oxygen species (ROS) production contributes to epithelial barrier dysfunction and mucosal remodeling in CRS.[11] Oxidative stress has been shown to activate redox-sensitive transcription factors such as NF-κB, thereby enhancing cytokine production and perpetuating chronic inflammation.[12] The higher oxidative burden observed in CRSwNP patients may reflect persistent inflammatory cell infiltration and enhanced ROS generation within polyp tissue.

Pro-inflammatory cytokines, particularly IL-6, TNF-α, and IL-1β, were significantly elevated in the CRSwNP group in our study. These cytokines play a central role in mediating mucosal edema, vascular permeability, leukocyte recruitment, and tissue hyperplasia. Elevated IL-6 levels have been linked with disease severity and recurrence in CRS, while TNF-α contributes to epithelial damage and remodeling processes.[13],[14] The strong positive correlation between cytokine levels and CT severity score observed in this study further reinforces the role of inflammatory mediators in disease progression and radiological severity. The association between oxidative stress and inflammatory cytokines observed in our study suggests a bidirectional relationship. ROS can stimulate

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cytokine release, and in turn, cytokines can enhance ROS production by activating inflammatory cells.[15] This vicious cycle may explain the more aggressive inflammatory phenotype observed in CRSwNP. Recent molecular studies have demonstrated upregulation of oxidative stress-related genes in nasal polyp tissues compared to non-polyp mucosa, supporting the biochemical findings observed in our patient cohort.[16]

Another important finding of the present study is the identification of elevated MDA and IL-6 as independent predictors of nasal polyp formation on multivariate analysis. This suggests that combined assessment of oxidative stress and inflammatory markers may have potential clinical utility in distinguishing CRS phenotypes. Emerging evidence supports the concept of biomarker-guided phenotyping in CRS, which may facilitate personalized treatment strategies, including the use of biologic therapies targeting specific inflammatory pathways.[17] Patients with high inflammatory burden and oxidative stress may represent a subgroup that could benefit from adjunct antioxidant therapy in addition to conventional medical and surgical management.

Our findings align with recent umbrella reviews emphasizing the central role of inflammatory mediators in CRS and highlighting the need for integrated biomarker evaluation rather than isolated parameter assessment.[18] By simultaneously examining oxidative stress markers and cytokines, this study provides a more comprehensive biochemical profile of CRS and underscores the complex interplay between redox imbalance and immune dysregulation.

Despite these significant findings, certain limitations should be acknowledged. The cross-sectional design limits causal inference between oxidative stress and polyp development. Additionally, tissue-level assessment of oxidative markers could provide deeper mechanistic insight compared to serum analysis alone. Future longitudinal and interventional studies are warranted to evaluate whether modulation of oxidative stress can alter disease severity or reduce recurrence in CRSwNP patients.

In conclusion, the present study demonstrates that CRSwNP is characterized by heightened oxidative stress and amplified pro-inflammatory cytokine activity compared to CRSsNP. The strong association between biochemical markers and radiological severity suggests that oxidative stress and inflammation are key contributors to polyp formation and disease progression. These findings support the potential role of combined oxidative and inflammatory biomarker assessment in improving CRS phenotyping and guiding targeted therapeutic strategies.

CONCLUSION

CRSwNP is characterized by heightened oxidative stress and amplified inflammatory cytokine activity. The significant association between oxidative imbalance and inflammatory mediators suggests their potential role as biomarkers for disease severity and polyp formation in chronic rhinosinusitis.

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