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Association of Oxidative Stress Biomarkers with Giant Cell Tumor of Bone and Local Recurrence: A Prospective Comparative Study

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ABSTRACT

Background and aim: Giant cell tumor of bone (GCTB) is a locally aggressive skeletal neoplasm with a high risk of local recurrence. Although oxidative stress has been implicated in tumor progression, its systemic role in GCTB remains poorly understood. This study evaluated systemic oxidative stress and antioxidant status in patients with GCTB and investigated their potential association with local recurrence.

Material and methods: In this prospective comparative study, 48 participants were enrolled, including 24 healthy controls, 20 patients with GCTB without recurrence, and 4 patients with local recurrence. Venous blood samples were collected at diagnosis from all participants and at the time of recurrence in recurrent cases. Serum malondialdehyde (MDA) and superoxide dismutase (SOD) activity were measured using standardized colorimetric and enzymatic assays.

Results: Patients with GCTB showed significantly higher serum MDA levels and significantly lower SOD activity than healthy controls ($p < 0.05$), indicating disruption of systemic redox homeostasis. Recurrent cases demonstrated the highest MDA levels and the lowest SOD activity; however, differences between recurrent and non-recurrent patients were not statistically significant.

Conclusions: GCTB is associated with increased systemic oxidative stress and reduced antioxidant capacity. Although recurrent tumors exhibited greater oxidative imbalance, these findings should be interpreted cautiously because of the limited number of recurrent cases. Larger prospective studies are required to determine whether oxidative stress biomarkers have prognostic value for predicting local recurrence in GCTB.

1. Introduction

Giant cell tumor of bone (GCTB) is a primary skeletal neoplasm characterized by locally aggressive behavior and a high propensity for local recurrence. Although traditionally classified as a benign tumor, GCTB frequently causes extensive osteolytic destruction and, in rare cases, pulmonary metastasis, underscoring the need for a deeper understanding of its biological behavior. Predominantly affecting the epiphyseal metaphyseal regions of long bones in young adults, GCTB accounts for a substantial proportion of primary bone tumors. Histologically, it is composed of neoplastic mononuclear stromal cells and osteoclast-like multinucleated giant cells that interact to promote bone resorption and tumor progression. Despite considerable advances in our understanding of GCTB, the molecular mechanisms underlying its locally aggressive phenotype and recurrent behavior remain incompletely elucidated.[1, 2] Recent studies have highlighted the pivotal role of the Rank/Rankl signaling pathway in the pathogenesis of GCTB, providing the rationale for targeted therapies such as denosumab in patients with unresectable or recurrent disease.[3] In addition, increasing evidence suggests that the tumor microenvironment plays a fundamental role in disease progression. The surrounding stromal and immune components may shift from maintaining normal bone homeostasis to promoting tumor growth, osteolysis, and local invasion, reflecting the dynamic Jekyll and Hyde nature of the tumor microenvironment.[4] Oxidative stress has emerged as an important contributor to tumor biology and is increasingly recognized as a key regulator of cancer initiation, progression, and therapeutic response. It results from an imbalance between the excessive generation of reactive oxygen species (ROS) and the capacity of endogenous antioxidant defense systems. Beyond being a mere consequence of tumor metabolism, oxidative stress actively modulates genomic stability, intracellular signaling pathways, cellular proliferation, and apoptosis.[5] Furthermore, cancer cells undergo metabolic reprogramming that enables them to survive under persistently oxidative conditions, thereby enhancing their invasive potential and adaptability.[6] Chronic oxidative stress has also been implicated in therapeutic

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resistance and prolonged survival of neoplastic cells, contributing to disease progression in several malignancies.[7] Despite substantial evidence linking oxidative stress to a wide range of human cancers, its role in Giant Cell Tumor of Bone remains insufficiently explored. In particular, little is known about longitudinal changes in systemic oxidative stress following surgical treatment or whether alterations in redox status are associated with local tumor recurrence. Clarifying these relationships may improve our understanding of GCTB biology and identify potential biomarkers for disease monitoring. Among the most widely investigated biomarkers of oxidative stress are malondialdehyde (MDA), a stable product of lipid peroxidation, and superoxide dismutase (SOD), a key enzymatic antioxidant responsible for scavenging superoxide radicals (O_2^-). Previous studies in bone tumors have consistently demonstrated elevated MDA levels together with reduced SOD activity, indicating systemic oxidative imbalance and impaired antioxidant defense.[1, 5] Whether similar alterations occur in GCTB and whether they correlate with recurrence remain uncertain. Therefore, the present prospective study was designed to evaluate systemic oxidative stress and antioxidant status in patients with Giant Cell Tumor of Bone by measuring serum MDA and SOD levels and to investigate their potential association with local tumor recurrence.

2. Material and methods

Study design and ethical approval

This prospective, longitudinal, comparative study was conducted at a tertiary care teaching hospital to investigate systemic oxidative stress in patients with Giant Cell Tumor of Bone (GCTB). The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC) prior to patient recruitment, and all procedures were performed in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants or their legally authorized representatives before enrollment. Patients with histopathologically confirmed GCTB who presented during the study period were consecutively recruited and prospectively followed after surgical treatment. Individuals who subsequently developed local recurrence during follow-up constituted the recurrence cohort without additional selection criteria, thereby minimizing selection bias.

Study population

A total of 48 participants were enrolled and categorized into three study groups. Group I consisted of 24 healthy age- and sex-matched volunteers who served as controls. Group II included 20 patients with histopathologically confirmed GCTB who underwent surgical treatment and remained free of local recurrence throughout the follow-up period. Group III comprised four patients who developed histologically confirmed local recurrence after primary surgical management. The unequal distribution of participants among the study groups reflected the natural incidence of recurrence observed during prospective follow-up rather than predetermined recruitment targets. Consequently, the relatively small number of recurrent cases should be considered when interpreting subgroup analyses and recurrence-related findings. (Table 1)

Table 1. Demographic profile of study population.

Parameters	Group I: Healthy Controls (n = 24)	Group II: GCT – No Recurrence(n = 20)	Group III: GCT – Recurrence (n = 4)
Sex (M:F)	1:2	1:3	1:3
Mean Age	26 ± 4 years	32 ± 2.3 years	28 ± 4.4 years
Location	-----	Distal Femur- 7 Proximal Tibia- 4 Distal Radius- 6 Proximal Femur- 2	Distal Radius-2 Proximal Tibia-1 Distal Femur- 1

Eligibility criteria

Patients with primary Giant Cell Tumor of Bone confirmed by histopathological examination were considered eligible for inclusion. Individuals with metastatic bone disease, secondary bone tumors, chronic systemic disorders known to influence oxidative stress (including diabetes mellitus and chronic inflammatory diseases), active infections, or those receiving antioxidant supplementation were excluded to minimize potential confounding effects on oxidative stress biomarkers.

Clinical evaluation and surgical management

All patients underwent comprehensive clinical assessment followed by standardized radiological evaluation, including plain radiography, computed tomography (CT), and magnetic resonance imaging (MRI), to determine tumor location, local extent, and surgical planning. The diagnosis of Giant Cell Tumor of Bone was confirmed histopathologically in every case. The primary surgical procedure consisted of extended intralesional curettage with or without bone grafting according to lesion characteristics. Local adjuvant techniques, including high-speed burring, phenol application, and polymethyl methacrylate bone cement, were used whenever clinically indicated to reduce residual microscopic disease and decrease the risk of local recurrence.

Biochemical analysis

Peripheral venous blood samples (5 mL) were obtained from all patients at the time of initial diagnosis prior to any surgical intervention. In patients who subsequently developed local recurrence, an additional blood sample was collected when recurrence was confirmed clinically and radiologically. Serum malondialdehyde (MDA) concentration was measured as an indicator of lipid peroxidation using a standardized thiobarbituric acid (TBA) colorimetric assay under acidic conditions, with absorbance recorded at 535 nm. Results were expressed as μmol/L. Superoxide dismutase (SOD) activity, representing systemic antioxidant capacity, was determined using an automated enzymatic assay (Randox Laboratories, UK). The assay was based on the inhibition of superoxide radical-mediated reduction of 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride (INT), and enzyme activity was expressed as U/mL. To ensure analytical reliability, all samples were analyzed in duplicate under blinded laboratory conditions. Internal quality control sera were included in each analytical run, and both intra-assay and inter-assay coefficients of variation were maintained below 10% throughout the study.

Follow-up and outcome assessment

Following surgery, all patients underwent scheduled clinical and radiological follow-up to monitor treatment response and detect local recurrence. Follow-up evaluations included physical examination together with serial plain radiographs and magnetic resonance imaging (MRI) whenever recurrence was clinically suspected. Local recurrence was defined as the reappearance of tumor at the primary surgical site based on compatible clinical findings and radiological evidence and was confirmed histopathologically whenever revision surgery was performed. The primary outcome of the study was the comparison of systemic oxidative stress markers between patients with Giant Cell Tumor of Bone and healthy controls. The secondary outcome was the assessment of the relationship between oxidative stress biomarkers and local tumor recurrence.

Statistical analysis

Statistical analyses were performed using appropriate statistical software. Continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are expressed as frequencies and percentages. Data distribution was assessed using the Shapiro–Wilk test prior to statistical analysis. Comparisons of demographic variables between study groups were performed using the Chi-square test or Fisher's exact test, as appropriate. Differences in serum MDA concentration and SOD activity among study groups were analyzed using Student's t-test or one-way analysis of variance (ANOVA) for normally distributed variables. Pearson's correlation analysis was performed to evaluate the relationship between oxidative stress and antioxidant biomarkers. A two-tailed p-value < 0.05 was considered statistically significant. Because only four patients developed local recurrence during follow-up, recurrence-related subgroup analyses should be interpreted cautiously owing to limited statistical power. Consequently, multivariable regression analyses were not performed, as the number of outcome events was insufficient to provide reliable statistical estimates.

3. Results

The biochemical analysis revealed a clear disruption of the redox balance in patients with Giant Cell Tumors compared to healthy controls. While patients who experienced recurrence showed higher levels of oxidative stress markers, these findings did not reach statistical significance when compared to the non-recurrence group.

Table 2. Oxidative stress markers in GCT cases (N=24).

Group	Number of Cases (n)	MDA (µmol/L) (Mean ± SD)	SOD (IU/mL) (Mean ± SD)
I - Healthy Controls	24	2.51 ± 1.05	165 ± 28
II - GCT - No Recurrence	20	5.62 ± 2.85	89 ± 29
III- GCT – At time of Recurrence	4	6.95 ± 3.90	68
GCT Total (All Cases)	24	5.84 ± 3.15	85 ± 32

Oxidative stress – MDA levels

Comparison between the total Giant Cell Tumor (GCT) group (n = 24) and healthy controls (n = 24) demonstrated a statistically significant increase in Malondialdehyde (MDA) levels ($p < 0.05$), indicating enhanced oxidative stress in patients with GCT. Furthermore, patients who developed local recurrence showed the highest mean MDA levels within the study cohort (6.95 µmol/L), suggesting a possible association between elevated oxidative stress and tumor recurrence. However, when Group II (No Recurrence) was compared with Group III (Recurrence), the difference in MDA levels did not reach statistical significance ($p > 0.05$).

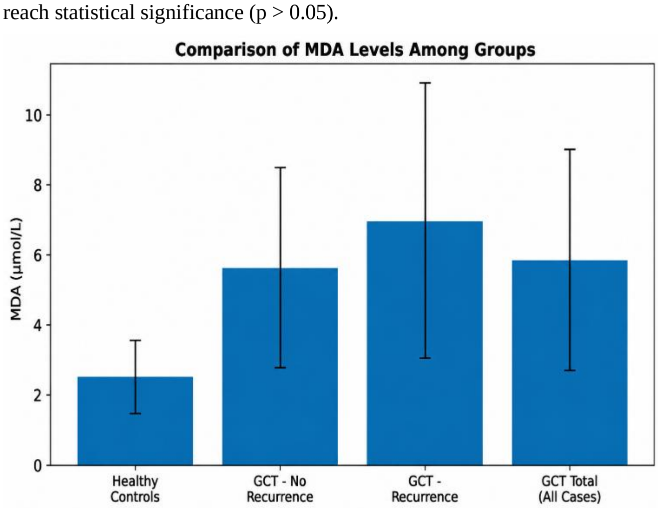

Fig. 1. Comparison of MDA levels among groups.

Antioxidant status – SOD levels

Superoxide Dismutase (SOD) activity was significantly reduced in the GCT group compared to healthy controls ($p < 0.05$), reflecting impaired antioxidant defense mechanisms in affected patients. Among all study participants, the recurrence group exhibited the lowest mean SOD activity (68 IU/mL), further supporting the presence of increased oxidative imbalance in recurrent disease. Nevertheless, despite this observed trend, the difference in SOD activity between the non-recurrence and recurrence groups was not statistically significant ($p > 0.05$), indicating that reduced antioxidant status alone may not be a statistically reliable predictor of recurrence in the present sample size.

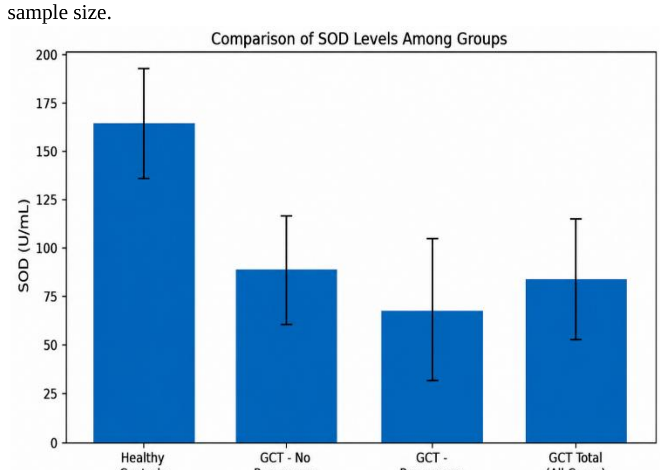

Fig. 2. Comparison of SOD levels among groups.

It is critical to emphasize that because the recurrence subgroup is extremely small (n = 4), any conclusions regarding the relationship between systemic oxidative stress and local tumor recurrence must be interpreted strictly as preliminary observations and trends rather than definitive statistical associations. While the descriptive data reveal an interesting pattern of heightened redox imbalance in these patients, the statistical power is insufficient to draw firm prognostic conclusions. Consequently, these findings serve primarily as a basis for hypotheses that require validation in much larger, multi-center prospective cohorts.

4. Discussion

The present study demonstrated that patients with Giant Cell Tumor of Bone (GCTB) exhibit a marked disturbance in systemic redox homeostasis, characterized by significantly elevated serum malondialdehyde (MDA) levels and reduced superoxide dismutase (SOD) activity compared with healthy controls. These findings indicate enhanced lipid peroxidation together with impaired antioxidant defense and support the growing evidence that oxidative stress contributes to the biological behavior of bone tumors. Comparable alterations have been documented in benign and malignant bone tumors, with elevated MDA levels accompanied by decreased antioxidant enzyme activity.[1] Notably, the MDA and SOD values reported in our GCT cohort were highly comparable to those described for benign bone tumors, reinforcing the concept that oxidative imbalance is not limited to malignant neoplasms but is also a feature of locally aggressive benign lesions. Although patients who developed local recurrence demonstrated the highest MDA levels and the lowest SOD activity, these differences did not reach statistical significance. This finding is most likely attributable to the limited number of recurrent cases included in the study rather than the absence of a biological association. Nevertheless, the consistent trend toward greater oxidative imbalance in recurrent tumors suggests that oxidative stress may contribute to tumor aggressiveness and recurrence. Similar observations have been described previously, where increasing oxidative stress was associated with tumor progression and disease severity.[1, 5] Partial normalization of oxidative stress markers has been observed following surgical treatment of benign bone tumors, suggesting that tumor burden itself substantially contributes to systemic oxidative imbalance.[2] Collectively, these findings support the hypothesis that persistent oxidative stress may reflect residual tumor activity or a biologically aggressive phenotype in recurrent GCTB. Reactive oxygen species (ROS) regulate multiple cellular processes involved in tumor development, including genomic instability, cellular proliferation, angiogenesis, apoptosis, and metabolic adaptation.[6] Oxidative stress has been shown to induce metabolic reprogramming within the tumor microenvironment, thereby enhancing the adaptive capacity of neoplastic cells and promoting their survival under hostile conditions.[6] Moreover, dynamic interactions between tumor cells and the surrounding microenvironment play a pivotal role in orchestrating tumor progression and contributing to disease recurrence.[4] Although GCTB is histologically classified as a benign neoplasm, its aggressive local behavior may, at least in part, be explained by ROS-mediated alterations in intracellular signaling pathways and stromal cell interactions. The increased serum MDA concentrations observed in the present study indicate enhanced lipid peroxidation caused by excessive ROS production. MDA is widely recognized as a reliable biomarker of oxidative damage because it reflects degradation of polyunsaturated fatty acids within cellular membranes.[1, 6] In contrast, the significant reduction in SOD activity indicates impairment of endogenous antioxidant defense mechanisms. As the primary enzymatic scavenger of superoxide radicals, SOD plays an essential role in maintaining intracellular redox balance. Depletion of this antioxidant defense permits ROS accumulation, thereby amplifying oxidative injury and potentially facilitating tumor progression.[7] Our findings are further supported by studies investigating oxidative stress in bone metabolism and skeletal tumors. Excessive ROS production has been shown to disrupt normal bone remodeling by disturbing the balance between osteoblastic bone formation and osteoclastic bone resorption.[8] Given that GCTB is characterized by excessive osteoclast activity and extensive osteolysis, oxidative stress may directly contribute to disease pathogenesis by enhancing RANKL-mediated osteoclastogenesis and activating inflammatory signaling pathways involved in bone destruction.[8] Furthermore, adaptation to chronic oxidative stress has been proposed to promote resistance to apoptosis and enhance tumor cell survival, potentially explaining the persistence of residual neoplastic stromal cells after surgery and contributing to local recurrence in GCTB.[7] Recent studies have increasingly focused on the molecular mechanisms underlying GCTB progression and recurrence. Current evidence indicates that neoplastic stromal cells, osteoclast recruitment, and cytokine-mediated osteolysis are key drivers of tumor development and disease progression.[3] The findings of the present study suggest that oxidative stress may represent an additional biological pathway involved in these processes. Consequently, assessment of oxidative biomarkers such as MDA and SOD may complement conventional clinicopathological parameters and potentially improve risk stratification for patients with GCTB. The present study has several limitations that should be acknowledged. Most importantly, the recurrence subgroup consisted of only four patients, substantially limiting statistical power and precluding robust subgroup analyses. Therefore, the observed association between greater oxidative imbalance and local recurrence should be considered preliminary and interpreted with caution. In addition, the study evaluated only two systemic oxidative stress biomarkers and did not investigate tissue-specific oxidative pathways or molecular regulators involved in tumor progression. Despite these limitations, this study provides novel evidence supporting the presence of systemic oxidative stress in Giant Cell Tumor of Bone and suggests a possible relationship between redox imbalance and tumor recurrence. Future multicenter prospective studies with larger patient cohorts, longer follow-up periods, and integration of oxidative biomarkers with molecular, genetic, and histopathological parameters are warranted to clarify the prognostic significance of oxidative stress and to determine whether modulation of redox pathways may represent a potential therapeutic strategy for patients with GCTB.[9-12]

5. Conclusion

The present study demonstrates that Giant Cell Tumor of Bone (GCTB) is associated with systemic oxidative imbalance, as evidenced by significantly increased serum malondialdehyde (MDA) levels and reduced superoxide dismutase (SOD) activity compared with healthy controls. Patients who developed local recurrence exhibited a trend toward greater oxidative stress; however, these differences did not reach statistical significance. Therefore, the observed findings should be interpreted cautiously and considered preliminary because of the limited number of recurrent cases. Nevertheless, the results support previous evidence suggesting that locally aggressive benign bone tumors are associated with alterations in systemic redox homeostasis. Larger multicenter prospective studies with longer follow-up and adequate statistical power are required to determine whether oxidative stress biomarkers can serve as reliable prognostic indicators of recurrence and to further clarify their role in the biological behavior of GCTB.

Conflict of Interest

The authors declared that there is no conflict of interest.

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