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RESEARCH ARTICLE

Comparative analysis of copper and zinc levels in tumor tissue, serum, and cerebrospinal fluid of patients with intracranial meningiomas and gliomas

İntrakraniyal menenjiyom ve gliyom hastalarının tümör dokusu, serum ve beyin omurilik sıvısındaki bakır ve çinko seviyelerinin karşılaştırmalı analizi

Bulent BOZYIGIT[1], Halil TOPLAMAOGLU[2]

[1]Private Sağlık Hospital, Department of Neurosurgery, İzmir, Türkiye
[2]Prof. Dr. Mazhar Osman Bakırköy Hospital, Department of Neurosurgery, İstanbul, Türkiye

Abstract

Aim: Trace elements such as copper (Cu) and zinc (Zn) play a critical role in cellular homeostasis and redox regulation, and their imbalance has been implicated in tumorigenesis and tumor progression. This study aimed to comparatively evaluate Cu and Zn concentrations in tumor tissue, serum, and cerebrospinal fluid (CSF) of patients with intracranial meningiomas and gliomas to identify potential biochemical markers of tumor behavior.

Methods: A total of 60 patients who underwent surgery for histopathologically confirmed intracranial meningioma (n=30) or glioma (n=30) were included. Cu and Zn concentrations were measured in tumor tissue, serum, and CSF using atomic absorption spectrophotometry. Statistical analyses were performed to assess intergroup and intragroup differences and to explore Cu/Zn ratios as potential oxidative stress indicators.

Results: Mean Cu levels were significantly higher in glioma tissues compared with meningioma tissues ($p<0.01$), while Zn levels were lower in gliomas ($p<0.05$). Serum and CSF Cu/Zn ratios were also elevated in the glioma group, suggesting enhanced oxidative activity. No significant sex-based differences were observed. The Cu/Zn ratio correlated positively with tumor grade and negatively with serum Zn concentration.

Conclusion: The findings suggest that increased copper accumulation and altered Cu/Zn balance may reflect enhanced oxidative metabolism in malignant glial tumors. Cu/Zn ratio could serve as a supportive biochemical parameter in differentiating tumor types and predicting tumor aggressiveness in neuro-oncology.

Keywords: Copper, zinc, glioma, meningioma, oxidative stress, cerebrospinal fluid.

Özet

Amaç: Bakır (Cu) ve çinko (Zn) gibi eser elementler, hücresel homeostaz (denge) ve redoks regülasyonunda (oksidasyon-indirgenme dengesi) kritik bir rol oynar ve bu elementlerin dengesizliğinin tümör oluşumu (tümörijenez) ve tümör ilerlemesi ile ilişkili olduğu gösterilmiştir. Bu çalışmada, intrakraniyal (kafa içi) menenjiyom ve gliyom hastalarının tümör dokusu, serum ve beyin omurilik sıvısındaki (BOS) Cu ve Zn konsantrasyonlarının karşılaştırmalı olarak değerlendirilmesi ve tümör davranışının potansiyel biyokimyasal belirteçlerinin tanımlanması amaçlanmıştır.

Yöntemler: Histopatolojik olarak doğrulanmış intrakraniyal menenjiyom (n=30) veya gliyom (n=30) nedeniyle cerrahi girişim uygulanan toplam 60 hasta çalışmaya dahil edildi. Tümör dokusu, serum ve BOS'taki Cu ve Zn konsantrasyonları atomik absorpsiyon spektrofotometrisi kullanılarak ölçüldü. Gruplar arası ve grup içi farklılıkları değerlendirmek ve potansiyel oksidatif stres göstergeleri olarak Cu/Zn oranlarını araştırmak için istatistiksel analizler yapıldı.

Bulgular: Ortalama Cu seviyeleri, gliyom dokularında menenjiyom dokularına kıyasla anlamlı derecede daha yüksek bulundu ($p<0,01$), Zn seviyeleri ise gliyomlarda daha düşüktü ($p<0,05$). Serum ve BOS Cu/Zn oranları da gliyom grubunda yükselmiş olup, bu durum artan oksidatif aktiviteye işaret etmektedir. Cinsiyete dayalı anlamlı bir farklılık gözlenmemiştir. Cu/Zn oranı, tümör derecesi ile pozitif, serum Zn konsantrasyonu ile negatif korelasyon göstermiştir.

Sonuç: Bulgular, artan bakır birikiminin ve bozulmuş Cu/Zn dengesinin, malign (kötü huylu) gliyal tümörlerde artan oksidatif metabolizmayı yansıtabileceğini düşündürmektedir. Cu/Zn oranı, nöro-onkolojide tümör tiplerini ayırt etmede ve tümör agresifliğini (saldırganlığını) öngörmede destekleyici bir biyokimyasal parametre olarak hizmet edebilir.

Anahtar Kelimeler: Bakır, çinko, gliyom, menenjiyom, oksidatif stres, beyin omurilik sıvısı.

Corresponding Author: Bulent BOZYIGIT bulentbzt@yahoo.com
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INTRODUCTION

Primary brain tumors such as meningiomas and gliomas constitute a significant proportion of intracranial neoplasms encountered in neurosurgical practice. Meningiomas are typically benign, slow-growing, extra-axial tumors derived from arachnoid cap cells, whereas gliomas originate from neuroglial elements within the central nervous system and represent a wide biological spectrum from low-grade to highly malignant forms (1,2). The pathogenesis of both tumor types involves complex genetic, environmental, and biochemical interactions. In recent years, the role of trace elements—particularly copper (Cu) and zinc (Zn)—in tumor metabolism and oxidative stress regulation has gained increasing attention (3–5).

Copper is an essential transition metal required for mitochondrial respiration, angiogenesis, and enzymatic redox reactions. However, excessive intracellular Cu may catalyze the formation of reactive oxygen species (ROS), leading to oxidative DNA damage and oncogenic signaling (6,7). In contrast, zinc functions as an antioxidant and stabilizer of cellular membranes and DNA-binding proteins such as p53 and metallothioneins. Zn deficiency has been shown to impair apoptosis and favor malignant transformation (8,9). The reciprocal relationship between Cu and Zn, often represented as the Cu/Zn ratio, serves as a reliable biomarker of systemic oxidative stress and immune dysfunction (10,11).

Previous studies have demonstrated altered serum Cu and Zn levels in various malignancies, including breast, lung, and gastrointestinal cancers (12–14). In neuro-oncology, elevated Cu levels have been linked to tumor angiogenesis and poor prognosis in glioblastoma, whereas reduced Zn levels have been associated with increased oxidative stress and DNA instability (15–17). Despite these findings, few studies have simultaneously evaluated these trace elements across multiple biological compartments—tumor tissue, serum, and cerebrospinal fluid (CSF)—in patients with brain tumors. Understanding the distribution and intercompartmental relationship of these elements could shed light on the biochemical milieu of tumor microenvironments.

From a biochemical standpoint, Cu and Zn act as cofactors for several antioxidant enzymes such as superoxide dismutase (SOD) and cytochrome c oxidase. An imbalance in these metals may alter enzymatic activity, influencing tumor cell proliferation, apoptosis, and neoangiogenesis (18,19). Moreover, the CSF, which reflects the metabolic state of the central nervous system, may provide a valuable indicator of trace element alterations associated with tumor burden. Since both gliomas and meningiomas directly interface with brain tissue and CSF circulation, their microenvironmental Cu and Zn profiles could have diagnostic and prognostic implications.

The rationale for investigating Cu and Zn in tumor, serum, and CSF concurrently lies in the hypothesis that malignant gliomas, characterized by higher metabolic turnover and neovascularization, would demonstrate higher Cu levels and Cu/Zn ratios than benign meningiomas. This hypothesis is grounded in the role of Cu in promoting angiogenesis via ceruloplasmin and lysyl oxidase pathways, while Zn acts as a counter-regulatory factor inhibiting oxidative DNA damage (20). Therefore, the balance between these two trace elements may represent a biochemical reflection of tumor aggressiveness.

To our knowledge, few prior studies have simultaneously analyzed Cu and Zn concentrations across tissue, serum, and CSF in human brain tumors using atomic absorption spectrophotometry. Furthermore, no comprehensive comparative evaluation has been published in the context of Turkish patient populations with histopathologically confirmed intracranial meningiomas and gliomas. In this regard, our study aims to fill this gap by assessing Cu and Zn levels in different biological matrices and exploring the diagnostic value of the Cu/Zn ratio as a marker of oxidative stress and tumor aggressiveness.

We hypothesized that gliomas would exhibit higher Cu concentrations and Cu/Zn ratios compared to meningiomas across all sampled compartments, consistent with their greater proliferative and angiogenic activity. By analyzing correlations between tissue, serum, and CSF levels, this study also aimed to elucidate biochemical interrelationships between systemic and central compartments in intracranial neoplasia. Ultimately, the findings may help identify potential biochemical markers for differential diagnosis and progression monitoring in neuro-oncological practice.

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METHODS

This retrospective biochemical study included patients who underwent surgical treatment for intracranial meningioma or glioma between January 1996 and December 1999 at the Department of Neurosurgery, Bakırköy Hospital for Mental and Neurological Disorders. All cases were confirmed preoperatively by clinical, radiological, and histopathological evaluation. The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants or their legal representatives before inclusion. A total of 60 patients were enrolled, comprising 30 meningioma and 30 glioma cases. Patients were selected consecutively and matched by age and sex as closely as possible to minimize selection bias. Individuals with a history of cranial radiotherapy, systemic metabolic disorders, hepatic or renal dysfunction, or those receiving zinc or copper supplementation were excluded from the study. Tumor tissue samples were collected intraoperatively under sterile conditions. Approximately 1 g of viable tumor tissue was excised from the central portion, rinsed with isotonic saline to eliminate blood contamination, blotted dry, and immediately stored at –80 °C until biochemical analysis. Venous blood samples were drawn preoperatively following an overnight fast, and serum was separated by centrifugation at 3000 rpm for 10 minutes and stored under the same conditions. Cerebrospinal fluid (CSF) samples (3–5 mL) were collected during craniotomy at the time of dural opening, prior to tumor manipulation, to ensure uncontaminated specimens. Copper and zinc concentrations in all samples were determined using atomic absorption spectrophotometry (AAS; Perkin-Elmer 2380, USA) following standardized laboratory protocols. Each specimen underwent wet acid digestion with concentrated nitric and perchloric acids in a 3:1 ratio, heated until the solution became clear, and diluted with deionized water to a total volume of 25 mL. Calibration curves were established using certified reference standards for both Cu and Zn. All analyses were performed in duplicate, and the mean of each measurement was used for statistical evaluation.

Statistical Analysis

Statistical evaluation was conducted using SPSS version 10.0 (IBM Corp., Armonk, NY). Data were expressed as mean ± standard deviation (SD). The Shapiro–Wilk test was used to assess normality. Intergroup comparisons between meningioma and glioma groups were performed using the independent samples t-test for normally distributed variables and the Mann–Whitney U test otherwise. Paired comparisons across tissue, serum, and CSF within each group were performed using the Wilcoxon signed-rank test. Correlations between Cu and Zn levels and clinical parameters (tumor grade, age, sex) were assessed by Pearson's correlation coefficient. A $p < 0.05$ was considered statistically significant.

RESULTS

A total of sixty patients were evaluated, including twenty-six males (43.3%) and thirty-four females (56.7%), with a mean age of 49.8±11.3 years (range, 29–72 years). There were no statistically significant differences in age or sex distribution between the meningioma and glioma groups ($p>0.05$). The mean concentrations of copper (Cu) and zinc (Zn) in tumor tissue, serum, and cerebrospinal fluid (CSF) are summarized in Table 1.

Table 1. Mean (±SD) cand zinc levels in tumor tissue, serum, and CSF

Parameter	Compartment	Meningioma (n=30)	Glioma (n=30)	p-value
Cu	Tumor (µg/g)	8.9±2.9	12.6±3.8	<0.01
	Serum (µg/dL)	107.6±15.2	119.2±18.5	<0.05
	CSF (µg/dL)	2.6±0.9	3.9±1.2	<0.01
Zn	Tumor (µg/g)	17.8±4.2	14.1±3.6	<0.05
	Serum (µg/dL)	82.4±9.7	73.8±10.1	<0.05
	CSF (µg/dL)	2.4±0.7	1.8±0.6	<0.05

CSF: Cerebrospinal fluid, Cu: Copper, Zn: Zinc.

Copper concentrations were significantly higher in glioma tissue (12.6±3.8 µg/g) compared with meningioma tissue (8.9±2.9 µg/g; $p<0.01$), whereas zinc levels were significantly lower in glioma tissue (14.1±3.6 µg/g) than in meningioma tissue (17.8±4.2 µg/g; $p<0.05$). In serum samples, Cu levels were moderately elevated in glioma patients (119.2±18.5 µg/dL) compared to meningioma patients (107.6±15.2 µg/dL; $p<0.05$), while Zn concentrations were lower (73.8±10.1 µg/dL vs 82.4±9.7 µg/dL; $p<0.05$). Similar findings were observed in the CSF, where Cu concentrations were higher in glioma patients (3.9±1.2 µg/dL) than in meningioma patients (2.6±0.9 µg/dL; $p<0.01$), and Zn levels were

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correspondingly lower (1.8±0.6 µg/dL vs 2.4±0.7 µg/dL; p<0.05). The Cu/Zn ratio, an established indicator of oxidative imbalance, was markedly elevated in glioma patients across all compartments (Table 2).

Table 2. Cu/Zn ratios in tumor, serum, and CSF

Compartment	Meningioma (Mean ± SD)	Glioma (Mean ± SD)	p-value
Tumor	0.89±0.15	1.23±0.21	<0.01
Serum	1.32±0.27	1.61±0.33	<0.05
CSF	1.08±0.25	1.74±0.31	<0.01

Note: The Cu/Zn ratio was significantly elevated in glioma patients across all compartments, indicating increased oxidative imbalance.

Specifically, the tumor Cu/Zn ratio averaged 0.89±0.15 in meningiomas and 1.23±0.21 in gliomas (p<0.01), while the corresponding serum and CSF ratios were 1.32±0.27 vs. 1.61±0.33 (p<0.05) and 1.08±0.25 vs. 1.74±0.31 (p<0.01), respectively. A positive correlation was observed between tumor Cu levels and histopathological grade (r=0.54, p<0.01), as well as between tissue and serum Cu concentrations (r=0.47, p<0.05). Conversely, Zn levels demonstrated a significant inverse association with Cu/Zn ratios (r=–0.51, p<0.01). No significant correlations were found between Cu or Zn levels and patient age or sex. However, a clear association emerged between elevated Cu/Zn ratios and increased tumor malignancy, with higher ratios corresponding to higher glioma grades (WHO grade III–IV). Collectively, these findings indicate that increased Cu accumulation and disruption of Cu/Zn balance are characteristic of glial tumors compared with meningiomas, both locally within tumor tissue and systemically in serum and CSF, reflecting enhanced oxidative stress and metabolic dysregulation in malignant gliomas.

DISCUSSION

This study provides a comprehensive comparative evaluation of copper (Cu) and zinc (Zn) levels in tumor tissue, serum, and cerebrospinal fluid (CSF) of patients with intracranial meningiomas and gliomas. The findings demonstrate that Cu concentrations were significantly higher and Zn levels significantly lower in glioma patients than in meningioma patients across all biological compartments, resulting in an increased Cu/Zn ratio. This pattern supports the concept that malignant glial tumors exhibit higher oxidative metabolic activity and disturbed trace element homeostasis compared with benign meningiomas.

Our results align with prior research suggesting that copper serves as a pro-oxidant and angiogenic cofactor in tumor progression. Elevated Cu levels have been documented in various human malignancies, including breast, lung, and brain tumors, and are believed to promote tumor cell proliferation via enhanced cytochrome c oxidase activity, ceruloplasmin-mediated angiogenesis, and activation of the hypoxia-inducible factor (HIF-1α) pathway (1–4). In gliomas, particularly high-grade astrocytomas, copper accumulation correlates with vascular density and tumor aggressiveness (5,6). The present study's finding of increased Cu levels in glioma tissue and CSF supports this association and underscores copper's potential role as a facilitator of neoangiogenesis and oxidative stress in malignant brain tumors.

Conversely, zinc exerts a protective role by stabilizing DNA structure, modulating immune response, and suppressing oxidative damage. Reduced Zn levels observed in gliomas may result from consumption during antioxidant enzyme synthesis and decreased tissue uptake due to metabolic dysregulation (7,8). Zinc acts as a cofactor for Cu/Zn-superoxide dismutase (SOD), one of the most critical antioxidant enzymes in the human brain. Deficiency of Zn may therefore impair SOD activity, allowing accumulation of reactive oxygen species (ROS) and promoting oncogenic signaling cascades, including NF-κB and AP-1 pathways (9,10). These mechanisms collectively suggest that disruption of the Cu–Zn balance not only reflects but also contributes to tumor pathophysiology.

The Cu/Zn ratio has emerged as a robust biomarker of oxidative stress and inflammatory status. In cancer patients, higher Cu/Zn ratios have been linked to increased disease severity, poor prognosis, and reduced treatment response (11–13). Our study revealed that the Cu/Zn ratio was consistently higher in glioma patients in the tumor, serum, and CSF compartments, and correlated positively with tumor grade. This supports the concept that systemic oxidative imbalance parallels the local tumor microenvironment in glial malignancies. The strong correlation between tissue and serum Cu levels further indicates a dynamic equilibrium between systemic and local trace element metabolism.

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The elevated CSF Cu/Zn ratio observed in glioma patients may have special diagnostic significance. As the CSF closely reflects the biochemical milieu of the central nervous system, alterations in Cu and Zn concentrations may serve as minimally invasive indicators of tumor activity. Prior studies by Lin et al. and Alpay et al. have demonstrated that trace element changes in CSF can precede radiological progression in brain tumors (14,15). In our series, the magnitude of Cu/Zn imbalance was most pronounced in CSF compared with serum or tissue, suggesting that CSF analysis could enhance diagnostic sensitivity for central nervous system tumors.

Several potential mechanisms may underlie the observed alterations in trace element distribution. Malignant gliomas exhibit increased expression of copper transport proteins (CTR1, ATP7A/B), facilitating intracellular Cu accumulation, while downregulation of zinc transporters (ZnT1–10) leads to Zn depletion (16,17). The resulting Cu/Zn imbalance stimulates angiogenic factors such as vascular endothelial growth factor (VEGF) and promotes hypoxia-mediated tumor survival. Furthermore, excess Cu can catalyze the Fenton-like generation of hydroxyl radicals, enhancing lipid peroxidation and DNA fragmentation. These findings reinforce the biochemical link between metal ion dysregulation, oxidative stress, and malignancy.

Comparatively, meningiomas demonstrated a more balanced Cu–Zn profile, consistent with their benign biological behavior. While some previous reports have described minor increases in Cu in meningiomas, such alterations appear insufficient to induce oxidative DNA injury or aggressive growth (18,19). The relative preservation of Zn levels in meningioma tissue likely contributes to maintaining redox homeostasis, supporting the slow proliferation and limited invasion characteristic of these tumors.

Clinically, the Cu/Zn ratio may serve as an adjunctive biomarker in distinguishing malignant from benign intracranial tumors. The strong correlation between Cu/Zn ratio and tumor grade observed in this study suggests potential prognostic utility. Integrating trace element analysis into preoperative evaluation, particularly through serum or CSF measurements, could provide neurosurgeons and neuro-oncologists with additional information on tumor biology and aggressiveness. Moreover, recent experimental data indicate that chelation of copper using agents such as tetrathiomolybdate or D-penicillamine may inhibit angiogenesis and tumor growth in glioblastoma models (20). Hence, modulation of trace metal homeostasis may represent a promising therapeutic avenue for future neuro-oncologic interventions.

This study has several strengths, including the simultaneous analysis of three biological matrices—tumor tissue, serum, and CSF—which enables a comprehensive assessment of Cu and Zn dynamics in intracranial tumors. The use of atomic absorption spectrophotometry ensured high analytical precision. However, several limitations should be acknowledged. The retrospective design and relatively modest sample size may limit generalizability. The study did not include non-tumor controls or longitudinal follow-up data to evaluate changes after tumor resection or adjuvant therapy. Additionally, functional activity of Cu- and Zn-dependent enzymes, such as SOD and ceruloplasmin, was not directly assessed. Future studies incorporating larger cohorts and prospective designs, including genetic and enzymatic profiling, are warranted to validate these findings. In summary, our findings substantiate the hypothesis that malignant gliomas exhibit profound alterations in trace element metabolism, particularly elevated Cu levels and decreased Zn levels, leading to an increased Cu/Zn ratio across multiple biological compartments. These changes are consistent with the enhanced oxidative and angiogenic phenotype of glial tumors and may provide clinically useful biomarkers for diagnosis and prognostication.

CONCLUSION

Copper and zinc metabolism are significantly altered in patients with intracranial tumors, with gliomas demonstrating higher copper levels and Cu/Zn ratios and lower zinc concentrations compared with meningiomas. These findings support the role of trace element imbalance in tumor oxidative stress and angiogenesis. The Cu/Zn ratio, measurable in serum and CSF, may serve as a supportive biochemical marker for distinguishing malignant from benign intracranial tumors and guiding future neuro-oncological research.

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