

Comparison of Serum Glucose Levels in Granulomatous and Nongranulomatous Mastitis

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ABSTRACT

This study aimed to compare serum glucose levels in histologically distinct granulomatous and nongranulomatous mastitis subtypes and to evaluate whether serum glucose functions as a systemic metabolic indicator reflecting the severity of tissue-level inflammation. Fifty-one cases (25 granulomatous and 26 nongranulomatous mastitis) diagnosed between 2022 and 2025 were retrospectively reviewed. Statistical analysis was performed using IBM SPSS v22. Independent samples t-test was used for comparisons, and ROC analysis was conducted to evaluate the diagnostic performance of serum glucose.

RESULTS: Serum glucose levels were significantly higher in the nongranulomatous group (104.12 ± 15.41 mg/dL) compared to the granulomatous group (95.46 ± 10.97 mg/dL; $p=0.026$). No significant differences were found regarding other parameters, including CRP, WBC, NLR, and SII. In ROC analysis, the area under the curve (AUC) for glucose was 0.638 ($p=0.090$).

In conclusion, serum glucose levels were significantly higher in nongranulomatous mastitis, reflecting a transient systemic metabolic stress response to acute tissue-level inflammation. However, given the nonsignificant discriminatory power in ROC analysis, glucose should not be considered an independent diagnostic biomarker; rather, it should be interpreted solely as an adjunctive metabolic indicator alongside definitive clinical, radiological, and histopathological findings.

Keywords: Blood Glucose, Stress Hyperglycemia, Inflammation Severity

Introduction

Mastitis is a pathology characterized by inflammation of the breast tissue, frequently encountered in clinical practice, and can present with a wide spectrum of histopathological findings (1). Based on its histopathological features, mastitis is divided into two main groups: “granulomatous mastitis”, characterized by lobule-centered granulomas, epithelioid histiocytes, and giant cells, and “nongranulomatous (nonspecific) mastitis”, characterized by diffuse inflammation and predominantly neutrophil-based infiltration (2).

Granulomatous mastitis is a rare but persistent disease, mostly seen in women of childbearing age, characterized by noncaseifying granulomas, giant cells, and chronic inflammatory cell infiltration (3, 4). A significant variant of this subtype, cystic neutrophilic granulomatous mastitis (CNGM), is characterized by small fatty cystic spaces within the granuloma and prominent neutrophil encirclement, and is frequently associated with *Corynebacterium* spp. (3, 5). In contrast, non-

granulomatous mastitis presents with acute or chronic inflammation without granuloma formation, as in classic infectious or lactational mastitis forms, and usually responds quickly to antibiotic treatment (6, 7).

Etiologically, granulomatous mastitis can develop due to autoimmune mechanisms, *Corynebacterium* infection, hormonal factors, or idiopathic causes (8, 9), while nongranulomatous mastitis is typically associated with bacterial infections and the lactation process (7, 10). The clinical course also differs significantly between the two subtypes; granulomatous mastitis presents a chronic, recurrent picture that can clinically mimic breast carcinoma (6, 11), while nongranulomatous mastitis is generally short-lived and responds quickly to treatment (7, 12).

In differential diagnosis, pathologies such as tuberculosis, fungal infections, sarcoidosis, granulomatous polyangiitis (Wegener's granulomatosis), foreign body reaction, periductal mastitis, and inflammatory breast cancer must be ruled out (3, 13, 14). Therefore, histopathological

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examination and biopsy are essential for definitive diagnosis (15).

In acute inflammatory processes, it is known that stress hyperglycemia, which develops to meet the body's increased energy needs, raises serum glucose levels (16). This metabolic response, triggered especially by the effect of pro-inflammatory cytokines, can vary depending on the severity of inflammation (17).

Comparing the systemic metabolic manifestations of histopathologically distinct inflammatory processes such as granulomatous and nongranulomatous mastitis may improve understanding of the relationship between inflammation severity and systemic metabolic response. Therefore, this study aimed to compare serum glucose levels between these two histopathological subtypes and to evaluate whether serum glucose reflects tissue-level inflammatory severity as a systemic metabolic indicator.

Materials and Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Non-Interventional Clinical Research Ethics Committee of Mardin Artuklu University (Date: April 7, 2026; Decision No: 2026/4-19).

Patient Selection and Study Design: In this retrospective study, biopsy and surgical materials (excisional, incisional, tru-cut) from patients diagnosed with mastitis at Mardin Training and Research Hospital between 2022 and 2025 were reviewed. A total of 51 cases were included in the study, which were categorized into two main groups based on their histopathological findings: granulomatous mastitis group (n=25) and nongranulomatous mastitis group (n=26). Within the granulomatous mastitis group 17 cases were classified as classic idiopathic granulomatous mastitis (IGM), while 8 cases were identified as CNGM variant.

Patients with incomplete medical records, those with a history of breast malignancy, or patients whose histopathological diagnosis was inconclusive were excluded from the study.

Localization (right/left/quadrant), radiological findings (BIRADS category), demographic data, size, and histological findings were noted for each case. Mastitis types were grouped as granulomatous (idiopathic/cystic neutrophilic) and nongranulomatous. Complete blood count,

acute phase reactant, and biochemical test results from the period one month prior to the procedure date were recorded. In the differential diagnosis of cases, hematoxylin-eosin (H&E) and Gram histochemical stains applied to paraffin sections were considered, along with culture results when necessary. Patient files with neoplastic lesions and those lacking sufficient clinical, laboratory, and evaluable materials were excluded from the study.

Statistical Analysis: Statistical analysis was performed using IBM SPSS Statistics v22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD). The Independent Samples t-test was used to compare laboratory parameters, between the two independent groups. The diagnostic performance of serum glucose was evaluated using Receiver Operating Characteristic (ROC) curve analysis and the Area Under the Curve (AUC) was calculated. A p-value < 0.05 was considered statistically significant.

Results

Clinical and Laboratory Findings: Statistical analysis revealed that serum glucose levels were significantly higher in the nongranulomatous mastitis group compared to the granulomatous mastitis group (104.12 ± 15.41 mg/dL and 95.46 ± 10.97 mg/dL, respectively; $p=0.026$). No significant differences were found between groups in terms of other inflammatory and hematological parameters, including CRP, leukocyte count, NLR, and SII. ROC curve analysis was performed to evaluate the diagnostic performance of serum glucose in differentiating nongranulomatous from granulomatous mastitis. The area under the curve was 0.638 (95% CI: 0.486–0.791; $p=0.090$), indicating limited and statistically nonsignificant discriminatory performance (Figure 1). Given that the result did not reach statistical significance, serum glucose demonstrates a limited and statistically nonsignificant discriminatory performance for direct diagnostic prediction between the two main mastitis subtypes (Table 1).

Histopathological Findings: Histopathological evaluation of the examined cases revealed that while granuloma formation was absent in the nongranulomatous mastitis group, a mixed type of inflammatory cell increase was detected, characterized by diffuse inflammation, significant tissue edema, and predominantly neutrophil-based acute inflammatory infiltration. In the granulomatous mastitis group, lobule-centered

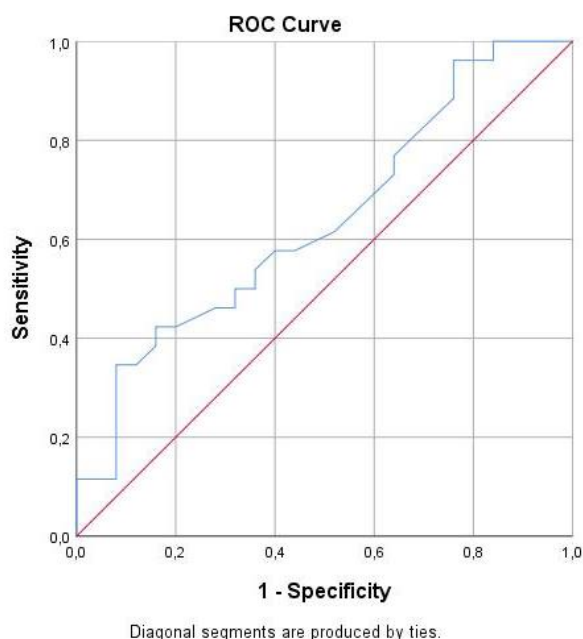


Fig. 1. Serum glucose level receiver operating characteristic (ROC) curve analysis was performed to differentiate nongranulomatous mastitis from granulomatous mastitis. The area under the curve (AUC) was calculated as 0.638 indicating a limited and statistically insignificant independent diagnostic performance for direct subtype differentiation

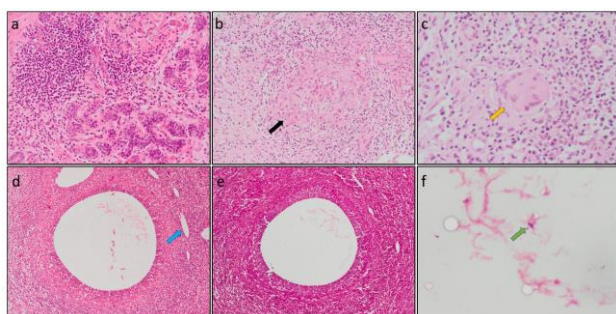


Fig. 2. Histopathological features of mastitis groups. a. Nongranulomatous mastitis; mixed inflammatory cell infiltration rich in lymphocytes and plasma cells in the interstitial area of the breast parenchyma (H&E, 20x). b. Idiopathic granulomatous mastitis; nonnecrotic granuloma formation (black arrow) consisting of neutrophils, lymphocytes, and histiocytes (H&E, 20x). c. Multinucleated giant cells (yellow arrow) associated with granulomatous inflammation (H&E, 40x). d. Cystic neutrophilic granulomatous mastitis; cystic spaces (blue arrow) appearing as lipid vacuoles surrounded by neutrophils at the center of granulomatous structures (H&E, 10x). e. Gram staining of cystic neutrophilic granulomatous mastitis (10x). f. Gram-positive bacilli (green arrow) identified within the lumina of the cystic spaces (Gram stain, 100x)

granuloma structures, epithelioid histiocytes, and multinucleated giant cells were typically observed. This group was accompanied by a predominantly

lymphocyte-based chronic inflammation picture. In some granulomatous cases, cystic spaces resembling lipid vacuoles surrounded by neutrophils were detected in the center of the granulomas (cystic neutrophilic granulomatous mastitis variant), and the presence of Gram-positive bacilli was demonstrated in these spaces (Figure 2).

Discussion

This study showed that serum glucose levels were higher in the nongranulomatous mastitis group compared to the granulomatous mastitis group. The limited discriminatory power of the ROC analysis suggests that glucose may be an indicator of the metabolic response associated with inflammation rather than a diagnostic marker on its own.

The most likely pathophysiological mechanism for the increase in glucose levels is stress hyperglycemia triggered by systemic inflammation. Increased cortisol, catecholamines, and proinflammatory cytokines especially such as TNF- α and IL-6 in acute inflammatory processes increase hepatic gluconeogenesis and lead to insulin resistance in peripheral tissues, causing an increase in serum glucose levels. This is considered an adaptive metabolic response to meet the increased energy requirements of the organism during infection and inflammation (18). Although inflammation is the most plausible explanation for the observed glucose differences in the present study, metabolic factors such as age and body mass index may also influence baseline glucose homeostasis and should therefore be considered when interpreting these findings.

Although the retrospective design of our study limited the ability to systematically control for these metabolic confounders across patient cohorts, extensive cross-sectional studies have demonstrated that advancing age strongly influences glucose metabolism, independently contributing to elevations in blood glucose and blood pressure (19). Furthermore, aging is associated with subclinical changes in body composition, and body mass index (BMI) is a major determinant of baseline glucose homeostasis and diabetes risk throughout adulthood (20).

The vast majority of nongranulomatous mastitis cases are acute and infectious in origin and are characterized histopathologically by significant neutrophil infiltration. In contrast, granulomatous mastitis is a chronic and mostly immune-mediated process characterized by noncaseifying granulomatous inflammation affecting the lobules (3, 21). In granulomatous mastitis, a chronic

Table 1: Comparison of Clinical and Laboratory Parameters Between Groups

Parameter	Nongranulomatous	Granulomatous	p-value
Glucose (mg/dL)	104.12±15.41	95.46±10.97	0.026*
CRP (mg/L)	18.26±29.72	24.48±30.38	0.545
WBC (103/ μ L)	9.47±3.03	9.17±2.30	0.695
NLR	3.13±1.55	2.99±2.20	0.789
SII	979.61±509.42	969.00±742.87	0.953

Data are expressed as mean $\pm$ standard deviation. CRP: C-Reactive Protein, WBC: White Blood Cell, NLR: Neutrophil-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index. *p < 0.05 indicates statistical significance

inflammatory response accompanied by lymphocytes, plasma cells, and histiocytes is prominent; while in nonspecific mastitis, acute inflammation and neutrophil infiltration are more dominant. Furthermore, even in the cystic neutrophilic granulomatous mastitis subtype described in recent years, bacterial agents, especially *Corynebacterium* species, have been shown to be associated with suppurative inflammation (22-24).

When these data are evaluated together, it is understood that a more pronounced acute and systemic inflammatory response develops in nongranulomatous mastitis; in contrast, a more limited, chronic, and localized inflammatory process predominates in granulomatous mastitis. The relative glucose elevation observed in the nongranulomatous mastitis group in our study can be interpreted as a reflection of the more pronounced metabolic stress response due to inflammation in this group.

Accurate initial differentiation between mastitis subtypes is clinically imperative due to the profoundly different management paradigms they necessitate, as granulomatous mastitis typically presents a chronic, recurrent clinical course (25). Recent clinical evidence highlights that targeted medical management specifically combined local intralesional steroid injections and topical steroid administration-provides a superior, sustained therapeutic response compared to traditional systemic oral steroid therapy (25). A comparative open-label study demonstrated that this localized infiltration of corticosteroids yields better and more sustained clinical responses, significantly lowering the need for aggressive surgical intervention (26). The profound clinical success of these localized steroid regimens, which boast lower recurrence rates and fewer systemic side effects, underscores the localized, immune-mediated, chronic nature of granulomatous mastitis (25). In stark contrast, the transient, high-intensity systemic metabolic shift observed in our cohort is a hallmark of the acute, nongranulomatous inflammatory cascade, which can help clinicians implement targeted therapies early and

avoid unnecessary systemic overtreatment or surgical excisions (25, 26).

Limitations: Our study has several limitations. First, the relatively small sample size and retrospective single-center design may restrict the statistical power and generalizability of the findings. Second, due to the lack of archival records, key confounding variables such as precise BMI, background insulin resistance, or undocumented metabolic comorbidities could not be corrected for with multivariate analyses. Third, recording laboratory parameters within the one-month period prior to biopsy leads to potential variability as systemic inflammatory markers and glucose levels fluctuate over time. Finally, precise standardization of fasting or fed conditions at the exact time of blood collection was not possible. Despite these limitations, given the extremely scarce literature on systemic metabolic changes in specific mastitis subtypes, this cohort represents a valuable preliminary investigation highlighting the need for future prospective, multicenter studies with synchronized real-time sampling.

In conclusion, serum glucose levels were significantly higher in nongranulomatous mastitis, reflecting a systemic metabolic stress response to acute tissue-level inflammation. While our results demonstrate that glucose should not be utilized as a standalone diagnostic biomarker to differentiate mastitis subtypes, it provides valuable clinical insight as an adjunctive metabolic indicator. Therefore, these transient glycemic shifts must be interpreted strictly in conjunction with definitive clinical, radiological, and histopathological findings.

Conflict of Interest: The authors declare no conflict of interest relevant to this study.

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