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THE USE OF OXIDATIVE STRESS BIOMARKERS IN PREDICTING ONCOGENIC TRANSFORMATION OF LEUKOPLAKIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract
The study investigates the prognostic significance of oxidative stress biomarkers in identifying oncogenic transformation potential in oral leukoplakia among patients with type 2 diabetes mellitus. The analysis included quantification of nitric oxide, 3-nitrotyrosine, malondialdehyde, and carbonylated proteins in blood serum, with concurrent assessment of thiol status and ceruloplasmin as antioxidant parameters. Biomarker dynamics were correlated with glycemic control stages. In decompensated patients, a critical elevation in oxidative markers was observed, notably a 300-fold increase in 3-nitrotyrosine, accompanied by a marked suppression of thiol groups and ceruloplasmin levels. The findings reflect sustained redox imbalance and biochemical destabilization of epithelial structures. The data indicate a direct association between intensified oxidative stress and epithelial transformation risk in leukoplakia under diabetic conditions.

Keywords: Type 2 diabetes mellitus, leukoplakia, oxidative stress, oncogenic risk, 3-nitrotyrosine, thiol status, ceruloplasmin, malondialdehyde, carbonylated proteins, predictive biomarkers, redox imbalance.

Introduction

Leukoplakia in patients with type 2 diabetes mellitus exhibits an increased frequency of dysplastic transformation and malignant conversion, associated with persistent redox disequilibrium. Hyperglycemia-induced oxidative stress

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promotes structural destabilization of the oral epithelium via peroxynitrite-mediated nitration, lipid peroxidation, and carbonylation of intracellular proteins. Elevated serum levels of 3-nitrotyrosine, malondialdehyde, and carbonylated proteins indicate sustained molecular degradation and activation of pro-oncogenic signaling cascades.

Parallel depletion of thiol reserves and ceruloplasmin confirms systemic exhaustion of antioxidant defense mechanisms. Quantitative shifts in redox biomarkers correspond with the degree of glycemic imbalance, particularly in subcompensated and decompensated metabolic states. These biochemical alterations correlate with early epithelial instability and enhanced proliferative indices in leukoplakic foci.

Oxidative biomarkers reflect cumulative metabolic damage and may serve as molecular predictors of malignant potential in diabetes-associated oral leukoplakia. The present study assesses the diagnostic relevance of redox imbalance in the stratification of oncogenic risk in precancerous mucosal lesions among patients with type 2 diabetes.

Oxidative stress is recognized as a fundamental molecular driver in the progression of premalignant oral lesions, particularly in patients with systemic metabolic disorders. In individuals with type 2 diabetes mellitus, chronic hyperglycemia induces a persistent redox imbalance that facilitates epithelial destabilization in leukoplakic lesions [1]. The overproduction of reactive oxygen and nitrogen species leads to oxidative modification of key cellular components, including DNA, membrane lipids, and structural proteins [2].

Elevated serum concentrations of malondialdehyde, nitric oxide, 3-nitrotyrosine, and carbonylated proteins have been reported in patients with leukoplakia associated with type 2 diabetes mellitus, indicating enhanced lipid peroxidation and nitrative stress [3]. These markers correlate with progressive dysplastic transformation of the oral epithelium and reflect early stages of oncogenic remodeling [4]. Notably, 3-nitrotyrosine has been identified as a direct product of peroxynitrite-induced nitration, serving as a specific indicator of oxidative protein damage in diabetic conditions [5].

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Simultaneously, antioxidant defense mechanisms are suppressed in diabetic individuals, with significant reductions in total thiol groups, ceruloplasmin, and enzymatic antioxidants such as superoxide dismutase [6]. These alterations compromise the mucosal barrier's ability to counteract pro-oxidant activity, leading to cumulative mutagenic pressure on basal epithelial cells [7]. A direct association has been demonstrated between low antioxidant reserve and increased proliferation indices in oral precancerous lesions [8].

Histopathological investigations confirm that leukoplakia in type 2 diabetic patients more frequently presents with severe dysplasia, basal cell hyperactivity, and loss of intercellular adhesion, all of which correlate with biochemical indicators of oxidative damage [9]. Integrating redox biomarkers into predictive models has been proposed as an effective strategy for risk stratification and early identification of malignant transformation in leukoplakia [10]. The specificity of oxidative stress indices for oncogenic potential in this subgroup justifies their inclusion in diagnostic protocols aimed at precision monitoring of diabetic mucosal pathology [11].

Recent studies support the clinical validity of oxidative stress panels, combining lipid peroxidation products, nitrative derivatives, and thiol depletion indices, as high-sensitivity predictors of epithelial carcinogenesis in oral tissues affected by diabetes-related metabolic instability [12]. The convergence of redox imbalance, impaired glycemic control, and mucosal inflammation forms a pathogenic triad promoting early molecular events in oral oncogenesis [13].

Materials and Methods

The study involved 97 individuals diagnosed with type 2 diabetes mellitus and clinically confirmed oral leukoplakia. Age range was 42 to 65 years. Male participants accounted for 53.6%, female for 46.4%. Patients were categorized into three groups based on glycemic control levels: compensated (n=36), subcompensated (n=34), and decompensated (n=27), with classification criteria based on daily mean glycemia and HbA1c levels. A control group (n=20) included age-matched healthy individuals without diabetes or oral epithelial pathology.

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Venous blood was collected in fasting state. Nitric oxide concentration was determined by colorimetric assay based on total nitrate and nitrite content using a commercial R&D Systems kit. 3-nitrotyrosine was quantified by ELISA (Hycult Biotech). Malondialdehyde levels were measured spectrophotometrically using the thiobarbituric acid method with detection of chromogenic adduct at 532 nm. Protein carbonyl content was evaluated by spectrophotometric assay at 270 and 363 nm using a modified Levine procedure.

Thiol status was determined by immunoenzymatic method (Thiol Status, Immunodiagnostik, Biotech). Ceruloplasmin concentration was measured using the Revin method. Superoxide dismutase activity was expressed in enzymatic units per milligram of protein. Glycemic parameters were measured enzymatically: glucose by the glucose oxidase method; glycated hemoglobin by the Knyazev protocol.

Statistical analysis was performed using the Mann–Whitney U-test. Significance level was set at $p<0.001$. All biochemical analyses were conducted under standardized laboratory conditions. Ethical approval was obtained prior to sample collection.

Results and Discussion

The biochemical profile of oxidative stress and antioxidant defense was evaluated in 97 patients diagnosed with oral leukoplakia in the context of type 2 diabetes mellitus. The study population was stratified into three groups based on metabolic compensation: Group I (compensated, n = 36), Group II (subcompensated, n = 34), and Group III (decompensated, n = 27). The control group (n = 20) included normoglycemic individuals without histopathological alterations in the oral mucosa. Analytical quantification of redox parameters revealed a statistically significant progressive deviation from baseline values in all diabetic subgroups ($p < 0.001$).

Serum nitric oxide levels exhibited a stepwise elevation from 12.4 ± 1.1 nmol/L in the control group to 34.9 ± 1.5 nmol/L in decompensated patients, indicating sustained activation of inducible nitric oxide synthase (iNOS). Concurrently, 3-nitrotyrosine concentrations, a marker of peroxynitrite-mediated nitration of

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aromatic amino acid residues, increased from 0.7 ± 0.03 µmol/L to 198.5 ± 7.9 µmol/L, exceeding the baseline level by more than 280-fold. These findings reflect a high level of nitrative stress and molecular disintegration of protein structures within the systemic circulation.

Malondialdehyde levels, determined via TBARS assay, rose from 2.91 ± 0.27 nmol/mL to 6.85 ± 0.42 nmol/mL across the glycemic strata, consistent with intensified lipid peroxidation. Carbonylated protein content, assessed spectrophotometrically at 270 nm and 363 nm, demonstrated a linear increase correlated with metabolic dysregulation, reaching 116.3 ± 3.1 a.u. in decompensated individuals.

Thiol group concentrations decreased significantly from 521 ± 18 µmol/L in the control cohort to 301 ± 21 µmol/L in Group III. This decline reflects depletion of the sulfhydryl-dependent redox buffering capacity, associated with both the loss of functional cysteine residues in plasma proteins and reduced glutathione pools. Ceruloplasmin levels, a secondary antioxidant and acute-phase reactant with ferroxidase activity, were markedly lower in diabetic patients, with a reduction from 25.4 ± 0.9 mg% to 12.9 ± 1.1 mg%. These data suggest cumulative oxidative exhaustion of metalloprotein-mediated neutralization systems.

The enzymatic activity of superoxide dismutase (SOD) displayed compensatory elevation in early metabolic imbalance but plateaued in the decompensated group, indicating functional saturation. Quantitative divergence in SOD levels, though statistically significant, did not exhibit predictive capacity for mucosal transformation risk in multivariate regression models.

Histological correlative data (excluded from this report) confirmed that elevated 3-nitrotyrosine and MDA concentrations were associated with high-grade dysplasia and keratinocyte hyperproliferation. In the decompensated group, 63% of lesions demonstrated non-homogeneous or erosive patterns, whereas in the compensated group, this phenotype was observed in only 19% of cases. Pearson correlation analysis revealed significant associations between 3-nitrotyrosine levels and histological grade ($r = 0.67$, $p < 0.01$), as well as between thiol status and cellular differentiation index ($r = –0.58$, $p < 0.01$).

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Diagnostic performance analysis yielded a threshold value of 3-nitrotyrosine >150 µmol/L for identifying high-risk leukoplakia with sensitivity of 84.2% and specificity of 79.5%. Receiver operating characteristic (ROC) curve analysis produced an AUC of 0.871 (95% CI: 0.79–0.94), confirming the discriminatory power of this biomarker in the context of redox-based oncogenic risk stratification.

The integrative pattern of redox imbalance, encompassing overproduction of reactive nitrogen and oxygen intermediates alongside suppression of thiol-dependent neutralizing capacity, delineates a mechanistic framework for early-stage oncogenic transformation in diabetic leukoplakia. The data confirm that the biochemical destabilization of mucosal structures in the diabetic milieu is not a secondary phenomenon but represents a primary molecular event with oncopathological implications.

Conclusion

The obtained data demonstrate that oxidative stress biomarkers, particularly 3-nitrotyrosine, malondialdehyde, and carbonylated proteins, exhibit significant predictive relevance for assessing oncogenic transformation potential in oral leukoplakia among patients with type 2 diabetes mellitus. The progressive elevation of pro-oxidant indices correlates with the degree of glycemic decompensation and parallels histopathological indicators of epithelial dysplasia. Simultaneously, the marked depletion of thiol reserves and ceruloplasmin confirms systemic antioxidant exhaustion, reinforcing the pathological role of redox imbalance in mucosal destabilization. Quantitative analysis identified 3-nitrotyrosine as a high-sensitivity marker for malignant risk assessment, with an established diagnostic threshold demonstrating robust specificity. These findings support the incorporation of oxidative biomarker panels into routine clinical evaluation of diabetic patients with oral potentially malignant disorders, enabling early risk stratification and targeted preventive monitoring.

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