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Characteristics of redox processes, thiol system and mucin in the tear fluid in type 2 diabetics

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Purpose: *To assess the characteristics of redox processes, thiol system and mucin in the tear fluid in patients with T2DM.*
Material and Methods: *Thirty type 2 diabetics (60 eyes) with ocular surface changes were included in the study. Patient eyes were divided into groups based on the bulbar conjunctival changes corresponding to the Nelson grade: group 1 (33 eyes with Nelson grade 2 to 3 changes in the bulbar conjunctiva) and group 2 (27 eyes with Nelson grade 0 to 1 changes in the bulbar conjunctiva). Tear lactate dehydrogenase (LDH), glucose-6-phosphate dehydrogenase (G6PDH), malate dehydrogenase (MDH), and glutathione peroxidase (GPX) activities and tear mucin, reduced glutathione (GSH) and oxidized glutathione (GSSG) levels were determined by routine techniques.*
Results: *We found alterations in tear redox reactions (LDH, G6PDH and MDH activities), GPX activity and thiol status (GSH and GSSG levels) in the setting of cytological conjunctival changes (i.e., different Nelson grades of squamous metaplasia) in type 2 diabetics. In addition, we found decreased tear mucin levels, which could be associated with alterations in the above biochemical processes and/or cytological conjunctival changes in patients of these groups.*
Conclusion: *Determining characteristics of tear redox reactions, glutathione system and mucin level can be considered as a method for monitoring the course of ocular surface disease based on the grade of squamous metaplasia of the bulbar conjunctiva in type 2 diabetics.*

Introduction

The ocular surface is exposed to oxidative stress through the environment and metabolic products [1].

Hyperglycemia promotes a state of systemic oxidative stress, in which disproportionate levels of reactive oxygen species (ROS) cause an increase in insulin resistance and β-cell dysfunction, thereby contributing to the progression of type 2 diabetes mellitus (T2DM) [2]. While functioning, cells and their components are subject to physiological oxidative stress from mitochondrial respiration associated with accumulation of intermediate metabolic products, superoxide (O2-) and hydrogen peroxide (H2O2) [3, 4].

Early neutralization of the intermediates that are formed (such as superoxide (O2-) and hydrogen peroxide (H2O2) [3, 4]) can prevent the accumulation of toxic oxygen radicals and further lipid peroxidation and cell injury. ROS can directly damage the tear lipid layer, corneal nerves, and the corneal and conjunctival epithelium and goblet cells. Dysfunction and apoptosis of these cells lead to decreased mucin production. Mucins are a group of glycocalyces produced by goblet cells and ocular surface epithelial cells, constituting the innermost layer of the tear film. The insufficient productions of mucins jeopardize the stability of the mucin layer and tear film, leading to a vicious cycle of DED [5].

The thiol system with its major thiol component, glutathione, maintains ocular oxygen homeostasis and

thiol status of proteins [3, 6, 7]. Given the intensity of oxidative stress-induced thiol oxidation in ocular tissues and biological fluids, the enzyme system for glutathione synthesis and regeneration of oxidized glutathione (GSSG) to reduced glutathione (GSH) and reduced phosphorylated form of nicotinamide adenine dinucleotide (NADPH) play a key role in maintaining the redox intracellular balance. Levels of glutathione and free sulfhydyl groups in tissues and fluids of the body (particularly, the eye) are indicators of the thiol status.

Glutathione is an intracellular peptide (the γ-L-glutamyl-L-cysteinyl-glycine) with diverse functions that include detoxification, antioxidant defense, maintenance of thiol status, and modulation of cell proliferation [3, 6, 8]. It is involved in maintaining the barrier function of the corneal endothelium, controlling normal hydration levels, protecting cell membrane integrity, and degrading xenobiotics agents [1].

In the mitochondria, glutathione is important in maintaining the redox potential [3, 7]. Glutathione peroxidase (GPX), a selenium-dependent enzyme, catalyses the reduction of lipid peroxides and hydrogen peroxide at the expense of glutathione. Reduced GSH levels are observed in cells subject to apoptosis, because glutathione regulates the redox cycle in thiol enzymes (e.g., stress kinases, caspases and NFκB). Nuclear factor-kappaB (NF-kappaB) is a transcription factor that may be triggered e.g., by hyperglycemia, which is relevant in the pathogenesis of ophthalmic diabetic complications [9]. Critically reduced glutathione levels contribute to a transition from apoptosis to necrosis (uncontrolled cell depth) [3, 10]. Not only the thiol system and glutathione-dependent enzymes but also the enzymatic antioxidant system (the latter including superoxide dismutase (SOD), GPX, and catalase) plays a major role in oxidative stress regulation [11].

Lactate dehydrogenase (LDH), malate dehydrogenase (MDH) and glucose-6-phosphate dehydrogenase (G6PDH) are the enzymes that play an important role in redox processes; the latter dehydrogenase reduces nicotinamide adenine dinucleotide phosphate (NADP) to NADPH that is required for the regeneration of oxidized glutathione.

A combination of ocular surface inflammatory disorder with T2DM-associated chronic hyperglycemia and, correspondingly, the magnitude and duration of oxidative stress, may affect the activation of the regenerative potential of corneal and conjunctival structures. There have been numerous publications on metabolic abnormalities in the presence of various pathogenic factors affecting the ocular system [1, 4, 9]. Nevertheless, biochemical characteristics of redox processes and thiol system in the presence of T2DM-associated ocular surface inflammation have been poorly investigated and should be further explored for assessing the biochemical processes, predicting treatment efficacy and monitoring treatment response.

The purpose of this study was to assess the characteristics of redox processes, thiol system and mucin in the tear fluid in patients with T2DM.

Material and Methods

Thirty type 2 diabetics (60 eyes) with ocular surface changes were included in the study. The cytologic changes in the bulbar conjunctiva were graded according to Nelson's grading system (1983) [12], and patient eyes were divided into groups based on the bulbar conjunctival changes: group 1 (33 eyes with Nelson grade 2 to 3 changes in the bulbar conjunctiva) and group 2 (27 eyes with Nelson grade 0 to 1 changes in the bulbar conjunctiva). The control group was composed of 23 eyes of 23 practically healthy individuals. The mean age of patients and controls was 62.47 ± 6.24 years.

Grades 0 and 1 were regarded as normal whereas grade 2 and 3 as abnormal cytology of the bulbar conjunctiva (i.e., typical for ocular surface damage). Irregular cell shape and nucleus size and positive cytoplasmic staining of epithelial cells, reduced number or absence of goblet cells, and widened intercellular spaces are signs of conjunctival squamous metaplasia [12].

Inclusion criteria were type 2 diabetics with an Ocular Surface Disease Index (OSDI) of 13–32 [13]; noninvasive tear break-up time (NIBUT) < 10 s as measured with Kanghua Ruiming's SLM-6E(A) Dry Eye Analyzer; Schirmer I test score < 10 mm/ 5 min; and grade 1 or 2 corneal and conjunctival fluorescein staining according to the Oxford scheme [14].

Eyes with a history of surgery or trauma, comorbidities (glaucoma, palpebral abnormalities, chalazion), contact lenses, and those with treatment with artificial tears, steroids or cyclosporine, and patients with systemic disorders like hyperthyreosis or rheumatic disorders were excluded.

Tear LDH [15], G6PDH [16], MDH [17], and GPX [18] activity and tear mucin [19], GSH and oxidized glutathione (GSSG) levels [20] were determined by routine techniques.

Tear fluid samples were collected without exogenous stimulation. Tear fluid was collected by placing a 7x12 mm filter paper strip (Filtrak No. 338; Filtrak, Niederschlag, Germany) into the lateral portion of the inferior conjunctival fornix for 5 minutes. The absorbed fluid was eluted from each strip into physiological saline and centrifuged at 3000 rev/min for 10 minutes. The supernatant was used for biochemical analyses.

Biochemical studies were conducted at the Biochemistry laboratory of SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine". Enzyme activity levels and glutathione and mucin levels in the supernatant were measured using an SF-26 (Lomo, St Petersburg, Russia) or Spekol-21 spectrophotometer (Analytik Jena, Jena, Germany).

The study was approved by the institutional bioethics committee (approval document No. 5 issued on November 10, 2021) and conducted in accordance with the ethical standards stated in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical analyses were conducted using Statistica 10.0 software (Statsoft, Tulsa, OK, USA). Data are presented as mean plus or minus standard deviation (SD). The Kolmogorov-Smirnov test was applied to test for normality. Parametric analysis of normally distributed data was performed using the two-tailed unpaired Student's t-test. The level of significance $p < 0.05$ was assumed.

Results

Tear LDH and G6PDH activities were higher in type 2 diabetics with Nelson's grade 2 to 3 squamous metaplasia as compared with type 2 diabetics with Nelson's grade 0 to 1 squamous metaplasia, but the difference was not statistically significant (Table 1). Of note that mean tear LDH and G6PDH activities in both patient groups were higher than in controls (tear LDH and G6PDH activities in group 1 were 38% and 34%, respectively, higher ($p < 0.01$), and in group 2, 23% and 21%, respectively, higher ($p < 0.05$) than in controls), which may indicate impaired cell membrane stability in corneal and conjunctival cells.

Tear MDH activities were higher in patients than in normal controls. Particularly, mean tear MDH activities in group 1 were 33% higher ($p < 0.01$), and in group 2, 21% higher ($p < 0.05$) than in controls (Table 2). There was, however, no significant difference in tear MDH activity between group 1 and group 2.

Because tear LDH, MDH and G6PDH activities were found to be significantly increased in diabetics, these activities may be considered a non-invasive biomarker of the severity of ocular surface disease based on the grade of squamous metaplasia of the bulbar conjunctiva [15].

Tear GPX activities were higher in type 2 diabetics than in normal controls. Particularly, mean tear GPX activities in group 1 were 32% higher ($p < 0.01$), and in group 2, 17% higher ($p < 0.05$) than in controls (Table 2). It is noteworthy that tear GPX activities in type 2 diabetics with grade 2 to 3 squamous metaplasia were 21% lower ($p < 0.05$) than in type 2 diabetics with grade 0 to 1 squamous metaplasia. This may indicate an exhausted antioxidant system component and is associated with depleted GSH and NADPH pools in the ocular tissue.

Thus, in groups 1 and 2, tear GSH level was 38% and 24% higher, respectively, (the difference was significant), and tear GSSG level was 58% ($p < 0.001$) and 28% higher ($p < 0.05$), respectively, than in normal controls (Table 3). This indicates a significantly impaired reducing potential of GSH in the bulbar conjunctiva of type 2 diabetics, with the impairment being more severe in the diabetics with Nelson grade 2 to 3 changes in the bulbar conjunctiva. That is, in group 2, tear GSH level and tear GSSG level were 22% higher and 19% lower, respectively, than in group 1, and these differences were statistically significant.

Mucin synthesis is altered in patients with altered redox processes and thiol status, which is indicated by low tear mucin levels in type 2 diabetics with squamous metaplasia. Particularly, in groups 1 and 2, tear mucin level was 34% ($p < 0.001$) and 20% lower, respectively, than in normal controls, and the differences were significant ($p < 0.001$ and $p < 0.05$, respectively; Table 4).

In addition, in group 2, tear mucin level was 22% higher than in group 1, and the difference was also significant ($p < 0.05$), which is likely to be due to a low number or the absence of goblet cells in diabetics with Nelson grade 2 to 3 squamous metaplasia. This resulted in low mucin production and, consequently, an alteration in the tear film mucin layer that plays an important role in the protection of conjunctival epithelial cells. Therefore, a vicious cycle arises, leading to the development of ocular surface damage in T2DM [4, 5].

Discussion

Studies have demonstrated links between hyperglycemia-induced oxidative stress, inflammation and the progression of T2DM [21].

Rehman and Akash [22] consider oxidative stress a most pivotal factor for the pathogenesis and development of T2DM. They describe it as a complex and multifactorial metabolic syndrome with characteristic abnormal metabolism in carbohydrates, fats and proteins leading to hyperglycemia and hyperlipidemia.

Apart from it been an evolving disease, Navarro and Mora [23] are more definitive on the kind of evolution that diabetes is undergoing. Specifically, the authors reported that it is evolving from metabolic disorder to an inflammatory condition. Oxidative stress has been reported as a known pathway in the pathogenesis of diabetic complications [24]. Hyperglycemic-induced oxidative stress is believed to increase the levels of pro-inflammatory proteins with infiltrated macrophages secreting inflammatory cytokines which leads to local and systemic inflammation [25]. Increased secretion of tumour necrosis factor alpha (TNF-alpha) has been observed to be linked to obesity-related insulin resistance and obesity is a risk factor for the development of T2DM [26].

Animal studies demonstrated that activities of redox enzymes (LDH, MDH, G6PDH, and GPX) in the cornea were significantly reduced (by 22%, 15%, 17.8% and 12.4%, respectively) in animals with acute conjunctivitis compared to normal controls [27, 28, 29].

GSH reducing potential in the cornea was significantly decreased in animals with streptozotocin-induced diabetes which developed experimental keratitis or conjunctivitis, which was indicated by increased GSSG and decreased GSH levels [30].

In addition, we have demonstrated previously that activities of redox enzymes (LDH, MDH, and G6PDH) were significantly increased, whereas GPX activity was significantly decreased in the tear fluid in animals with streptozotocin-induced diabetes which developed experimental or conjunctivitis. Activities of LDH, MDH,

G6PDH and GPX were, however, significantly decreased in the cornea in these animals, indicating alterations in cell membrane integrity and enzymatic component of the ocular antioxidant system [31].

We also found alterations in redox reactions (LDH, MDH, G6PDH and GPX activities), GPX activity and GSSG and GSH levels in the tear fluid in the presence of cytological conjunctival changes (different Nelson grades of squamous metaplasia) in type 2 diabetics. Moreover, tear mucin levels were found to be decreased in these patients, which is likely to be associated with alterations in the biochemical processes and/or cytological conjunctival changes.

The current study's findings confirmed our previous findings of alterations in redox reactions and thiol status in the tear fluid in animals with streptozotocin-induced diabetes. Our finding of a decreased level of tear mucin in type 2 diabetics discloses a mechanism of tear film stability alteration and ocular surface damage, contributing to the knowledge on the pathogenesis of dry eye disease in T2DM.

Conclusion

Tear LDH and G6PDH activities in type 2 diabetics with grade 2 to 3 squamous metaplasia were 38% and 34%, respectively, higher ($p < 0.01$) than in controls, indicating alterations in redox processes in the ocular surface in type 2 diabetics.

Type 2 diabetics with Nelson grade 2 to 3 squamous metaplasia showed a significantly greater alteration in antioxidant system function compared to those with Nelson grade 0 to 1 squamous metaplasia. In the former patients, tear GPX activity was 21% lower ($p < 0.05$), GSH level, 22% lower ($p < 0.05$), and GSSG level, 20% higher ($p < 0.05$), than in the latter patients, indicating an exhausted detoxification system of the ocular surface.

In type 2 diabetics with Nelson grade 2 to 3 squamous metaplasia and Nelson grade 1 to 0 squamous metaplasia, tear mucin level was 34% ($p < 0.001$) and 20% ($p < 0.05$) lower, respectively, than in normal controls, which may indicate an altered function of conjunctival goblet cells. Determination of tear mucin levels will enable a better understanding of disease patophysiology and developing more effective methods of diagnosis and treatment.

Determining characteristics of tear redox reactions, glutathione system and mucin level can be considered as a method for monitoring the course of ocular surface disease based on the grade of squamous metaplasia of the bulbar conjunctiva in type 2 diabetics.

Table 1. Tear lactate dehydrogenase and glucose-6-phosphate dehydrogenase activities in type 2 diabetics with Nelson grade 2 to 3 versus 0 to 1 squamous metaplasia of the bulbar conjunctiva

Biochemical characteristics	Statistics	Normal controls (n=23)	Group 1 (Nelson grade 2 to 3) (n = 33)	Group 2 (Nelson grade 0 to 1) (n = 27)
LDH, μMol/min·l^{-1}	M±m p1 %1 p2 %2	4.36±0.28 - 100 - -	6.03±0.43 <0.01 138.3 - 100	5.34±0.38 <0.05 122.5 >0.05 88.6
G6PDH, μMol/min·l^{-1}	M±m p1 %1 p2 %2	8.45±0.53 - 100 - -	11.32±0.87 <0.01 134.0 - 100	10.21±0.64 <0.05 120.8 >0.05 90.2

Note: LDH, lactate dehydrogenase; G6PDH, glucose-6-phosphate dehydrogenase; SD, standard deviation; p1, significance of difference compared to controls; p2, significance of difference between groups 1 and 2; %1, percentage difference compared to controls; %2, percentage difference between groups 1 and 2

Table 2. Tear malate dehydrogenase and glucose-6-phosphate dehydrogenase activities in type 2 diabetics with Nelson grade 2 to 3 versus 0 to 1 squamous metaplasia of the bulbar conjunctiva

Biochemical characteristics	Statistics	Normal controls (n = 23)	Group 1 (Nelson grade 2 to 3) (n = 33)	Group 2 (Nelson grade 0 to 1) (n = 27)
MDH, μMol/min·l^{-1}	M±m p1 %1 p2 %2	38.62±2.45 - 100 - -	51.28±3.60 <0.01 132.8 - 100	46.75±3.06 <0.05 121.1 >0.05 91.2
GPX, μMol/min·l^{-1}	M±m p1 %1 p2 %2	3.54±0.20 - 100 - -	2.42±0.16 <0.001 68.4 - 100	2.93±0.18 <0.05 82.8 <0.05 121.1

Note: G6PDH, glucose-6-phosphate dehydrogenase; MDH, malate dehydrogenase; SD, standard deviation; p1, significance of difference compared to controls; p2, significance of difference between groups 1 and 2; %1, percentage difference compared to controls; %2, percentage difference between groups 1 and 2

Table 3. Tear levels of reduced glutathione and oxidized glutathione in type 2 diabetics with Nelson grade 2 to 3 versus 0 to 1 squamous metaplasia of the bulbar conjunctiva

Biochemical characteristics	Statistics	Normal controls (n = 23)	Group 1 (Nelson grade 2 to 3) (n = 33)	Group 2 (Nelson grade 0 to 1) (n = 27)
GSH, μMol/l	M±m p1 %1 p2 %2	114.25±9.32 - 100 - -	71.26±5.12 <0.05 62.4 - 100	87.05±6.20 <0.05 76.2 <0.05 122.2
GSSG, μMol/l	M±m p1 %1 p2 %2	38.59±3.16 - 100 - -	60.95±4.52 <0.001 157.9 - 100	49.20±3.25 <0.05 127.5 <0.05 80.7

Note: GSH, reduced glutathione; GSSG, oxidized glutathione; SD, standard deviation; p1, significance of difference compared to controls; p2, significance of difference between groups 1 and 2; %1, percentage difference compared to controls; %2, percentage difference between groups 1 and 2

Table 4. Tear mucin level in type 2 diabetics with Nelson grade 2 to 3 versus 0 to 1 squamous metaplasia of the bulbar conjunctiva

Biochemical characteristics	Statistics	Normal controls (n = 23)	Group 1 (Nelson grade 2 to 3) (n = 33)	Group 2 (Nelson grade 0 to 1) (n = 27)
Mucin, g/l	M±m	1.62±0.12	1.07±0.07	1.30±0.08
	p1	-	<0.001	<0.05
	%1	100	66.0	80.2
	p2	-	-	<0.05
	%2	-	100	121,5

Note: SD, standard deviation; p1, significance of difference compared to controls; p2, significance of difference between groups 1 and 2; %1, percentage difference compared to controls; %2, percentage difference between groups 1 and 2

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Disclosures

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Abbreviations: *DED, dry eye disease; G6PDH, glucose-6-phosphate dehydrogenase; GPX, glutathione peroxidase; GSH, reduced glutathione; GSSG, oxidized glutathione; LDH, lactate dehydrogenase; MDH, malate dehydrogenase; T2DM, type 2 diabetes mellitus; NADPH, reduced phosphorylated form of nicotinamide adenine dinucleotide*