Evaluation of changes in tear film parameters in patients with advanced and end-stage chronic kidney disease

Zmiany w parametrach filmu łzowego u chorych w zaawansowanym i schyłkowym stadiach przewlekłej choroby nerek

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Abstract:

Aim: The dry eye syndrome is a common reason for medical appointments. Many factors, including local and systemic disorders or drugs contribute to its occurrence. The aim of the study was to assess changes on the ocular surface in patients with advanced (G4) and end-stage (G5) chronic kidney disease.

Material and methods: Depending on the estimated glomerular filtration rate (eGFR) and the treatment used, the subjects were divided into three groups. Group I: patients with end-stage chronic kidney disease on haemodialysis (chronic kidney disease stage 5); Group II: patients with markedly decreased eGFR (chronic kidney disease, stage 4); Group III: people with normal eGFR. Tear film break-up time test and Schirmer II test were performed. Conjunctival hyperaemia, conjunctival/corneal calcifications as well as fluorescein and lissamine green staining were assessed.

Results: There were no differences in the prevalence of conjunctival hyperaemia (p = .147), bulbar conjunctival calcifications (p = .484) and corneal calcifications (p = .687). The study groups differed significantly with regards to the prevalence of pingueculae in the bulbar conjunctiva (p = .024), Schirmer II test and tear film break-up time. Corneal staining with fluorescein and lissamine green showed no differences between the study groups (p = .433 and p = .140, respectively). Both staining methods yielded significant differences with regards to the surface of the bulbar conjunctiva (p = .002 and p = .0001, respectively).

Conclusions: Advanced chronic kidney disease and haemodialysis negatively affect the tear film. Conjunctival abnormalities appear to be associated with degenerative processes which occur more frequently in patients with chronic kidney disease. There was no difference in the condition of ocular surface and tear film parameters between patients with G4 and G5 of chronic kidney disease.

Key words: chronic kidney disease, ocular surface, tear film break-up time, Schirmer test, fluoresceine, lissamine green.

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Introduction

The issue of lacrimal deficiency in ocular pathology was first presented by Schirmer in 1903 (1); in 1933, Sjögren described the advanced form of the disorder and called it keratoconjunctivitis sicca (2). Chronic lacrimal deficiency with subsequent chronic inflammation disrupt the morphology of ocular
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The eGFR value in Group I did not exceed 15 mL/min/1.73 m² (mean value of 6.48 mL/min/1.73 m²). The mean duration on haemodialysis was 34 months (range of 7 to 72 months). In Group II, the eGFR value did not exceed 30 mL/min/1.73 m² (mean value of 15.38 mL/min/1.73 m²). In Group III, the eGFR equal to or above 60 mL/min/1.73 m² (mean value of 80.92 mL/min/1.73 m²).

A statistical analysis did not reveal differences in prevalence of bulbar conjunctival hyperaemia between the groups (p = .147). The symptom was observed in 11 eyes (22.92%) from Group I, 4 eyes (8.33%) from Group II and 8 eyes (16.67%) from Group III. There was no difference in prevalence of bulbar conjunctival calcifications between Groups II and III (p = .484). Bulbar calcifications were found in 3 eyes (6.25%) from Group II and 6 eyes (12.5%) from Group III. In Group I, there were no cases of bulbar conjunctival calcifications. The prevalence of corneal calcifications was comparable across the three groups (p = .687). It was demonstrated in 18 eyes (37.50%), 16 eyes (33.33%) and 14 eyes (29.17%) from groups I, II and III, respectively.

There was a difference (p = .024) between the groups in prevalence of pigueculae on the bulbar conjunctiva. It was present in 25 eyes (52.08%) from Group II, 19 eyes (39.59%) from Group I and only 12 eyes (25.00%) from Group III. There were also differences in Schirmer II test between group I and III (p = .0001) as well as group II and III (p = .003), with comparable Schirmer test findings in groups I and II (p = 1.000)

The mean values of Schirmer test were 8.23 ± 3.94 mm (median 7.00 mm), 9.02 ± 5.65 mm (median 8.00 mm) and 12.31 ± 4.55 mm (median 12.00 mm) in groups I, II and III, respectively. There were significant differences in TBUT between groups II and III (p = .007) and groups II and III (p = .017) with comparable TBUT findings in groups I and II (p = 1.000). The mean TBUT was 7.38 ± 4.33 s (median 6.00 s) in Group I, 7.65 ± 4.70 s (median 6.00 s) in Group II and 8.90 ± 2.63 s (median 9.0 s) in Group III.

There were no differences in corneal epithelial staining with fluorescein and lissamine green between the groups (p = .433 and p = .140, respectively). Corneal fluorescein staining was demonstrated in 21 eyes (43.75%) from Group I, 15 eyes (31.25%) from Group II and 17 eyes (35.42%) from Group III. Corneal lissamine green staining was demonstrated in 6 eyes (12.5%) from Group I, 8 eyes (16.67%) from Group II and 2 eyes (4.17%) from Group III. On the other hand, there were differences in conjunctival staining with fluorescein and lissamine green between the groups. Conjunctival fluorescein staining was observed more often in groups I (34 eyes, 70.83%) and II (35 eyes, 72.92%) than in group III (20 eyes, 41.67%).
Discussion

Disturbance of calcium and phosphate metabolism observed in patients with CKD and confirmed in many research reports might have a considerable effect on eye surface. Morphological changes mainly include small calcifications, involving both the cornea and conjunctiva. Initially, it was reported that such changes occur in patients receiving long term haemodialysis. This study, however, reveals that they are also present in patients with earlier stage CKD, who do not need renal replacement therapy yet.

Calcium deposits are usually localized in the limbo-conjunctival area, within the palpebral fissure. This is associated with the fact that tear film is a medium for the ocular surface epithelium to return carbon dioxide from the interpalpebral area to the environment. When pH changes into alkaline, the substance gets less soluble. Consequently, calcium salts in the cornea, corneal limbus and conjunctiva get precipitated. Vignanelli and Stucchi confirmed that the process is promoted by elastogenic degenerative changes in subepithelial connective tissue (5). Calcifications found in dialysed patients are both dystrophic and “metastatic” (6). An article published by Porter and Crambie (7) provides a more accurate grading system for corneoconjunctival calcifications. Their severity scale used involves: no calcifications, conjunctival calcifications and corneoconjunctival calcifications of varying degree.

Corneoconjunctival calcifications can also be associated with other disorders. Özdemir et al. noted that the degree of calcifications correlates with dry eye symptom severity in patients on haemodialysis (8). Hsiao et al. confirmed a significant association between the presence of calcifications, their severity and mortality of patients on haemodialysis (9).

Calcifications usually develop over a longer time. There are very few reports on relatively rapid development, lasting only a few months. The process starts with calcific deposits forming the girdle of Vogt. Next, they turn into central corneal opacity. The final stage of the progress involves extensive deposits forming band keratopathy. The progression of these changes was shown to be associated with increased plasma phosphate levels and later also with an increased free calcium ion level (10).

While conducting a study in patients on haemodialysis, Bogorodzki et al. observed not only calcifications but also perilipase vascularization at the corneal limbus, which penetrated 1–3 mm into the cornea. They concluded that these abnormalities did not affect visual acuity (11). In our study, there were no between-group differences in prevalence of corneal calcifications. Interestingly, although pingueculae were present more often in patients on haemodialysis than in other patients with CKD, it was not true for bulbar conjunctival calcifications. As noted previously, conjunctival degenerative changes contribute to the formation of calcifications. A relatively short duration of renal replacement therapy (34 months) in Group I might account for these findings. On the other hand, good quality nephrological care might have positively affected the ocular surface of CKD patients. It should be noted that most studies on corneal and conjunctival changes in CKD patients were conducted in the 1970’s and 1980’s. Since then, not only have we become more knowledgeable in the pathophysiology of CKD progression but first of all, we have improved methods of renal replacement therapy, which has enabled elimination of multiple complications.

Authors of early publications on ocular changes in patients on long-term haemodialysis reported intensive conjunctival hyperaemia as a common symptom (7, 12). Klaassen-Broekem and van Bijsterveld identified three types of hyperaemia, i.e. pingueculitis, extensive conjunctival hyperaemia and extensive conjunctival and episcleral hyperaemia. In an attempt to identify the underlying causes, they concluded that it resulted from disturbances of calcium and phosphate metabolism (13, 14). Berylne and Shaw (15) confirmed a relationship between the presence of hyperaemia and increased levels of inorganic phosphates. There were no cases of hypercalcaemia in their study group. A decreased blink reflex (16, 17), exhaled air, containing di- and tri-methylamine which is “harmful” for the ocular surface, hydrogen peroxide as well as nitrogen oxide, which has vasodilatory properties, are believed to contribute to the “red eye” symptom (18). Interestingly, Berylne and Shaw (15) did not observe an increase in conjunctival hyperaemia in patients with advanced stages of CKD, which seems surprising when considering significant changes in the quality and quantity of tear film in CKD patients. It was probably explained by Klaassen-Broekem, who demonstrated an association between the degree of conjunctival hyperaemia in patients with CKD and the presence of calcium deposits on the ocular surface (13). Since an increased prevalence of corneal or conjunctival calcifications was not confirmed, the involvement of calcium salts, found in the ocular surface epithelium, in conjunctival hyperaemia in patients with renal failure cannot be ruled out.

Current studies on the condition and parameters of tear film in patients on haemodialysis have brought in other interesting observations. Increased osmolality of the tear film prior to haemodialysis, followed by its slight hemodialysis-induced decrease, observed by Charlton et al., can provide an explanation for a decreased level of urea in tears, which is initially high. The same study also implies that the patients hardly complain about ocular dryness due to potential protective, moisturising and mucolytic effect of urea on ocular surface epithelium, in conjunctival hyperaemia in patients with renal failure cannot be ruled out.

Berylne and Shaw (15) noted that patients with CKD demonstrate excessive keratosis of the conjunctival epithelium (22), whereas Jung (23), Özdemir (8) and Türk-
ců (24) showed epithelial metaplasia, decreased TBUT and decreased basic tear secretion in eyes of patients with CKD. Additionally, Demir et al. found that the severity of squamous epithelial metaplasia of the conjunctiva was associated with the duration of haemodialysis (25). Furthermore, it has been pointed out that patients in advanced stages of CKD can feel discomfort due to changes in tear secretion and distribution on ocular surface, which are secondary to conjunctival degeneration, including pinguecula and pterygium. Interestingly, in our study, patients with stage 4 (Group II) and 5 (Group I) CKD developed pingueculae of bulbar conjunctiva more often than CKD-free controls. Decreased TBUT in patients with advanced stages (G4 and G5) of chronic kidney disease, observed in our study, has been confirmed by other published studies (8, 23). The underlying causes of TBUT abnormalities in patients on haemodialysis include a reduced count of conjunctival goblet cells (22), conjunctival squamous epithelial metaplasia (8, 24) and increased incidence of demodicosis (26).

Benitez-del-Castillo et al. proposed that basic tear secretion results from constant, “subconscious” stimulation of the corneal surface (27). They observed abnormal values of the Schirmer test in patients in advanced stages (G4 and G5) of chronic kidney disease. In this case, decreased basic tear secretion may be associated with neural conduction disturbance leading to development of peripheral neuropathy and reduced corneal sensitivity, as demonstrated by Kirshan (28).

The reason why we used lissamine green was that its staining range was comparable to that of rose Bengal but the tolerance profile was better (29). Positive lissamine green staining of bulbar conjunctiva indicates focal epithelial metaplasia (30), which was also confirmed for rose Bengal (8). Single fluorescent-in-stained foci in the bulbar conjunctiva, observed in patients with stages 4 and 5 CKD might have been caused by micro-califications which damage the epithelium. Abrams (12) made similar observations with regards to the occurrence corneal changes. However, this explanation seems insufficient as we did not demonstrate bulbar conjunctival calcifications in patients on haemodialysis. Submicroscopic nature of conjunctival calcifications may be taken into consideration but an impaired blinking reflex might provide an alternative explanation (19, 20). It is difficult to explain this phenomenon due to lack of noticeable changes within corneal epithelium.

**Conclusions**

Advanced CKD and haemodialysis used in end stage CKD negatively affect the quality and amount of tear film. Conjunctival abnormalities appear to be associated with degenerative processes, which occur significantly more often on the ocular surface of patients with CKD. We did not demonstrate a difference in the condition of ocular surface and tear film parameters between patients with G4 and G5 of chronic kidney disease.

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