INFLUENCE OF GLAUCOMA ON DIABETES-INDUCED CHANGES IN THE ANTERIOR OCULAR SEGMENT

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INFLUENCE OF GLAUCOMA ON DIABETES-INDUCED CHANGES IN THE ANTERIOR OCULAR SEGMENT (Abstract). **Aim:** To monitor the influence of glaucoma on the changes caused by diabetes in the anterior ocular segment. **Material and methods:** Prospective, comparative clinical study, which included the patients with glaucoma and diabetes assessed at the Iaşi “Sf. Spiridon” Hospital, “Euro Medi Center” Clinic and “Oftaprof” Clinic. The study included a number of 142 patients, divided into two groups: 67 patients with glaucoma and diabetes (study group) and 75 patients with diabetes mellitus (control group). Upon enrollment the patients were subjected to a complete assessment of their ophthalmologic and metabolic status. Monitored aspects: prevalence of lens changes, extent of ocular surface disease and identification of the changes in corneal biomechanical parameters in the patients with glaucoma and diabetes. **Results:** In both monitored groups, the cortical lens changes prevailed, both at the beginning and at the end of the study, with no statistically significant differences between groups (p>0.05). The risk of developing lens changes reaches 50% in the patients who have had diabetes for 20 years. In the patients in the study group, tear secretion was significantly lower at the end of the study (Schirmer’s test values 11.61 vs. 10.67 mm, p=0.045). Tear film instability was present in 37.3% of the patients. Corneal hysteresis (CH) and corneal resistance factor were significantly reduced in the group with glaucoma and diabetes, as compared to the group with diabetes (p=0.001). **Conclusions:** There is significant ocular surface disease in the patients with glaucoma and diabetes, as compared to those with diabetes alone. Glaucoma and the number of antiglaucoma drugs are associated with a significant reduction in tear secretion. The association of glaucoma resulted in the reduction in CH and corneal resistance factor in the patients with glaucoma and diabetes as compared to the healthy ones. **Keywords:** POAG, CH, CRF, SCHIRMER’S TEST, OSDI QUESTIONNAIRE.

Diabetes and glaucoma are two chronic conditions with a significant impact on visual function, both determining degenerative changes at ocular level. In the patients with diabetes and in those with glaucoma, the vascular factor has an important role, in both conditions abnormalities in retrobulbar vascular flow and retinal microcirculation being present (1). These are a problem mainly in the developed countries with high life expectancy. Most complications involve both the anterior and the posterior segment of the eye, but numerous clinical studies only describe the presence of changes caused by diabetic retinopathy. A range of other ocular changes at the level of the lens and cornea are not well documented and that this study aims to highlight them (2). Studies in the
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literature have shown that lens changes are a cause of severe visual impairment in diabetic patients, the most frequent changes occurring at cortical and posterior subcapsular level, the risk increasing with diabetes duration and poor glycemic control (3,4). Ocular surface changes associated with diabetes have been carefully studied over the last decades. Clinical studies have shown that diabetes is associated with lacrimal gland dysfunctions, reduction in reflex tear secretion and tear film break-up time of the (5,6). Other studies aimed to demonstrate the role of diabetes and glaucoma in the changes in ocular biomechanical parameters, mostly with contradictory results. It was found that these properties determined by ORA (Ocular Response Analyzer) are affected by glucose level, hyperglycemia determining dysfunctions of the corneal endothelium (7,8,9). This study aimed to assess the influence of glaucoma on the diabetes-induced ocular changes in the anterior segment (lens, ocular surface, corneal biomechanics).

MATERIAL AND METHODS

This is a prospective, observational and comparative clinical study carried out in the Ophthalmology Clinic I of the Iași “Sf. Spiridon” Hospital in collaboration with the “Euro Medi Center” and “Oftaprof” Clinics. The study was carried out in accordance with the ethical principles of the Declaration of Helsinki, the protocol being explained in detail to each patient, and obtaining the informed consent for the participation in the study. The inclusion criteria were: age over 35 years, confirmed diagnosis of primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG), open cameral angle (III-rd, IV-th degrees) according to Schaffer’s classification, associated mixed type 1/type 2 diabetestes, assessed based on blood sugar and glycosylated hemoglobin levels. The exclusion criteria were: patients with very advanced glaucoma, secondary glaucoma (pseudoexfoliative, pigmentary, neovascular, cortisone-induced), absence of DM and patients not attending the subsequent checkups. The participants were therefore divided into two groups: study group (including patients with glaucoma and diabetes) and control group (patients with diabetes). After enrollment the patients were assessed every 3-6 months.

The protocol for patient assessment included a comprehensive eye and vision examination: visual acuity, intraocular pressure (IOP) measured by Goldmann aplanotonometry, biomicroscopy of the anterior segment, central corneal thickness (Tomey ultrasound pachymeter), computerized recording of visual field by using the glaucoma programs of Humphrey perimeter, indirect gonioscopy with Goldmann three mirror lens, eye fundus exam with Volk lens and retinal photography with Zeiss Fundus Camera. The identification of changes in the retinal nerve fiber layers and the C/D (cup/disc) ratio were carried out by using the Zeiss Cirrus HD OCT device. Lens status after pupil dilation was assessed by biomicroscopy of the anterior segment and by photographic documentation using a Topcon biomicroscope provided with a digital camera, three images being obtained per eye and the type and extension of lens opacity was recorded using as a rough guide the LOCS (Lens Opacities Classification System), the most frequently used system in clinical studies. Both upon enrollment and at the end of the study, every study patient was subjected to Schirmer I test (without anesthesia), BUT (break-up time) and to fluorescein staining. At the end of the follow-up period, the patients filled in an OSDI (Ocular Surface
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Disease Index) questionnaire, used to obtain various aspects related to the ocular surface disease. The OSDI includes 3 subscales: ocular discomfort (5 questions), ocular symptoms during daily activities (4 questions) and environmental factors (5 questions); the OSDI total score is assessed on a scale of 0 to 100: 0-12 normal, 13-22 moderate, 33-100 severe. By means of the ORA (Ocular Response Analyzer), the corneal biomechanical parameters have been assessed: CH, corneal resistance factor (CRF), IOPcc (corneal-compensated intraocular pressure) and IOPg (Goldmann- correlated intraocular pressure). Diabetes was assessed by determining the serum level of blood sugar and glycosylated hemoglobin (HgA1c). Diabetes and glaucoma duration and the number of antiglaucoma drugs were noted. The statistical analysis of the data was performed by using the SPSS 18.0 statistics software. Of the used statistical tests, we mention: the ANOVA test, t student (statistically significant at p<0.05), chi² test, Pearson correlation, Krushall –Wallis correlation, ROC curve (prognostic factor) and the Kaplan –Meier curve (probability, hazard).

RESULTS

The study group included 142 patients with DM, divided into two groups: group I - 67 patients (47%) with diabetes and POAG and group II (controls) - 75 diabetic patients (53%) without glaucoma. The statistical analysis utilized data from one eye only, the most affected one. Gender distribution showed a prevalence of females in both groups. Mean age was 65.58+/− 7.87 years, the groups being homogenous in this respect. Diabetes duration was of 11.01+/− 8.28 years in group I and 13.32+/−9.94 years in group II. Glaucoma duration was of 5.75+/− 4.54 years. According to Hodapp classification, depending on the Mean Deviation level, the patients in group I presented moderate glaucoma both at the beginning and at the end of the study. Only one case was classified as advanced glaucoma (MD> -12db) and was not taken into account in the final evaluation. Of the total number of patients, 22.38% had NTG and 77.62% POAG. At the beginning of the study we found that 68.7% of patients in group I and 57.3% of patients in group II had statistically significant cortical lens changes (p=0.036). The other changes (subcapsular, nuclear, corticonuclear) were present in much lower percentages (12%, and 14.7%, respectively).

At the end of the study, in both groups, the percentage of cortical lens changes had decreased, but there was an increase in the percentage of cortical nuclear opacities, the changes at nuclear level determining cataract worsening and impaired visual function (fig. 1).

In the studied cases, multiple linear regression analysis revealed that gender, age, diabetes and glaucoma duration are not good predictors of lens changes (p>0.05), a positive cumulative correlation being found in only 3.4% of the patients. At the end of the study the glycosylated hemoglobin level was significantly lower in the patients with cortical changes both in group I (7.03 vs. 6.61%, p=0.02) and in group II (7.30 vs. 6.91%, p=0.025). Kaplan Meier curve highlighted an increased risk of developing lens changes, more than double in patients suffering from diabetes mellitus for almost 20 years. The probability of developing lens changes reaches the level of 50% in the patients suffering from diabetes mellitus for 10 years or from primitive open-angle glaucoma for 5 years (fig 2).
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Fig. 1. Group structure according to lens modifications at the beginning and at the end of the study (Group I=glaucoma and diabetes; Group II=diabetes)

Fig. 2. Probability of lens changes depending on diabetes and/or glaucoma duration

Tear secretion test (basal Schirmer’s test) values ranged from 3 to 25mm, a severe value (3 mm) being recorded in one patient (0.7%) low tear secretion values (5-10mm) in 35 patients (26.4%). The average values of Schirmer’s test had significantly decreased towards the end of the study in the group I patients (11.61 vs. 10.67; p=0.045) as compared to group II. Tear film break-up time (BUT) ranged from 3 to 21 seconds, tear film instability being recorded in 37.3% of the patients (fig. 3). The ocular surface disease index (OSDI) ranged from 8.33 to 39.58, highlighting a severe damage in 6% of the cases and moderate in 16.4%. Similarly, to tear secretion, in group I patients there was a significant decrease in BUT (9.33 vs. 8.57, p=0.028), but without significant differences in group II, the control group.

The number of glaucoma drugs ranged from 1 to 3. There was an association of 2, 3 drugs in 40% of the patients in the study group. At the end of the study, tear secretion test revealed significantly lower values in those on 3 or more glaucoma drugs (p=0.037). In case of BUT and OSDI there were no statistically significant differences according to the number of glaucoma drugs. The multivariate analysis highlights that Schirmer’s test, BUT, OSDI questionnaire and the IOP level are good predictors in the determinism of the degree of ocular damage (p=0.014):
The assessment of the changes in corneal biomechanical parameters included 156 subjects, 49 subjects with diabetes and glaucoma (90 eyes) selected from group I and 17 subjects with diabetes mellitus (34 eyes) selected from the control group (group III), who were able to be assessed by ORA. These groups of subjects were compared to a group of 46 subjects (92 eyes) with primary open-angle glaucoma (group II) and a group of 48 normal subjects (96 eyes) (group IV). The statistical analysis took into account the measurements in both eyes. Assessment of central corneal thickness (CCT) highlighted no statistically significant differences among the study groups in the right eye (p=0.561) or in the left eye (p=0.455). Goldmann-measured IOP, Goldmann-correlated IOP, corneal-compensated IOP had significantly higher values in groups II and III as compared to group IV (p<0.005), with no differences between the two eyes. Both in the right eye (p=0.001) and in the left eye (p=0.001), CH values were significantly lower in the patients in group I and II, as compared to group IV. The CRF values were significantly lower in the patients with G+/- DM as compared to the other groups (p=0.011), with no statistically significant differences between the two eyes (fig. 4).

The comparison between CH and IOP revealed statistically significant, direct moderate correlations only in group III. The comparison between CH and the CCT highlights direct correlations (if the value of the correlation coefficient is closer to +1 there is an all the higher dependence of the two parameters, direct correlation, and if closer to -1, it shows that there is also a very high dependence between the parameters, but an indirect one) with moderate intensity, statistically significant in all groups (r=+1,
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The comparison between CRF and Goldmann-measured IOP shows that there is a direct, moderate, statistically significant correlation in group II only \((r=+0.579, \ p=0.001)\). Moreover, the comparison of CRF and CCT values shows direct, moderate, statistically significant correlations in groups I, II, IV \((r=+1, \ p<0.05)\) and indirect correlations in group III \((r=-1, \ p<0.05)\). In the diabetic patients with POAG (group I) as compared to those without POAG (group II), we noticed significantly lower values of IOP measured by the Goldmann tonometer and of CRF in both eyes. The level of glycosylated hemoglobin did not significantly influence the values of corneal biomechanical parameters in any of the groups \((p>0.05)\). The multivariate linear analysis highlights age, CCT, CH and CRF as good predictors in the determinism of glaucoma+/- diabetes mellitus.

DISCUSSION

The common epidemiological and pathogenic features, the complications involving the ocular structures with irreversible effect on vision have determined the serious assessment of diabetes and glaucoma in numerous studies, some of them with contradictory results. The most controversial result is the one of the Ocular Hypertension Treatment Study (OHTS), the authors concluding that diabetes is a protective factor for glaucoma, a low percentage of the monitored patients with diabetes developing glaucoma \((3.1\%)\) \((10)\). Other studies find associations between diabetes and glaucoma, suggesting that diabetes is a risk factor for glaucoma \((11,12)\). A retrospective study carried out on 46 patients with glaucoma and diabetes (92 eyes), highlighted a (marginal statistically) significant influence of the presence of non-proliferative diabetic retinopathy in glaucoma progression \((13)\). This risk is explained by the vascular factor, as the long evolution of diabetes can compromise the vascular, glial and retinal neuronal elements, being associated to a high risk in the development and progression of primary open-angle glaucoma \((14,15)\). However, most of the studies in the literature only assess the role of diabetes in developing glaucoma; to our knowledge, there are no studies assessing the risk caused by glaucoma on the frequent changes induced by diabetes at ocular level. Knowing that diabetic retinopathy and cataract are the most frequent causes of visual impairment and decreased quality of life in the patients with diabetes, glaucoma association could additionally influence the progression of these changes. The studies in literature have shown that lens changes have an increased prevalence in diabetics \((3,4)\). The results of this study are mostly similar to those in the literature. The groups were homogenous in terms of age \((65)\), the female gender prevailed, the average diabetes duration was of 11 years and of the glaucoma of 5 years. The statistical analysis of the studied cases showed an increased prevalence of cortical lens changes over the study period \((68.7\% \text{ in group 1 and } 57.3\% \text{ in group 2})\) with statistically significant differences between groups \((p<0.05)\). These changes seem to be rather related to diabetes (average duration - 11 years), but they can also be related to age (average age: 65). There were no statistically significant differences between the analyzed groups; therefore, glaucoma did not significantly influence the results. The assessment of ocular surface disease showed a significant degree of ocular surface disease in the patients with G+DM vs. those with DM alone, tear secretion and
tear film break-up time being significantly lower at the end of the study. Glaucoma and the number of glaucoma drugs were associated with a significant decrease in tear secretion (p=0.037). Schirmer’s test, BUT, OSDI questionnaire proved to be good predictors of the degree of ocular involvement. Similarly to the studies in the literature comparing the degree of ocular surface disease in patients with glaucoma as compared to those without glaucoma, we found a higher degree of ocular damage due mostly to glaucoma therapy (2,16). The studies in literature assessing the biomechanical properties in patients with diabetes report controversial results. Some studies state that diabetes causes a CH decrease as compared to healthy subjects, others that CH and CRF are significantly increased in patients with poor blood sugar control, as compared to the healthy subjects with good control (8,9,17). CH decrease is explained by the alteration of collagen components, thus reducing the corneal dumping phenomenon, and CH increase is due to the rigidity of collagen structure of the cornea in diabetics (20). The reasons for such contradictory results are probably the differences in age and CCT, but also the diversity of DM types and their severity (in some studies most patients had type 2 diabetes, while others had a similar number of patients with type 1 and 2 diabetes). Similarly, the results obtained in our study show that glaucoma association determined a reduction of CH in the diabetics with glaucoma as compared to those without glaucoma and healthy control subjects. This is explained by the known fact that in glaucoma there is a reduction in corneal viscosity and corneal dumping phenomenon. The altered collagen structure may be additive to the effect of a thicker cornea, thereby further increasing the measured IOP, which can lead to an overestimation of the true IOP with Goldmann aplanotonometer in the population with diabetes (17).

The present study has some limitations. The obtained results cannot be extrapolated to global level mainly because of the small number of patients included in the study and of the short monitoring period. The absence of a comparative OSDI (ocular surface disease index) score in the group with DM is another limitation. In the groups assessed for changes in corneal biomechanical parameters, there are no data regarding the level of HgA1c, blood sugar upon enrollment and at the end of the study, and degree of glaucoma in the control groups.

CONCLUSIONS
In our study the cortical lens changes prevailed at the beginning of the study in both groups. The probability to develop lens changes is of 50% in the patients with 10-year duration of DM or 5-year duration of the POAG. There was a significant degree of ocular surface disease in the patients with G+DM as compared to those with DM alone. The presence of glaucoma and the number of glaucoma medications are associated with a significant decrease in tear secretion (p=0.037). The association of glaucoma determined a decrease in CH and CRF corneal biomechanical parameters in the diabetic patients with glaucoma as compared to those without glaucoma and healthy control subjects. Age, CCT, CH, CRF and Goldmann- measured IOP are good predictors in the determinism of glaucoma +/- diabetes. In the future, a longer monitoring period and database extension could lead to the improvement of the results obtained in this study.
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REFERENCES


