CLINICAL CHANGES AND BIOMETRIC DIFFERENCES IN PATIENTS WITH PRIMARY OPEN ANGLE GLAUCOMA AND DIABETES

Anca Pantalon\textsuperscript{1,2}, Crenguța Feraru\textsuperscript{1,2}, D. Chiseliță\textsuperscript{1,2*}, F. Târcoveanu\textsuperscript{1,2}

“Grigore T. Popa” University of Medicine and Pharmacy Iasi
Faculty of Medicine
1. Surgical Department of Surgery
“Sf. Spiridon” County Clinical Emergency Hospital Iasi
2. Ophthalmology Clinic
*Corresponding author. E-mail: chiselita.dorin@gmail.com

CLINICAL CHANGES AND BIOMETRIC DIFFERENCES IN PATIENTS WITH OPEN ANGLE GLAUCOMA AND DIABETES (Abstract). Aim of study was to emphasize the clinical changes and biometric alterations that appear in primary open angle glaucoma (POAG) patients if diabetes was associated. Material and methods: The study was designed in a cross-sectional manner, between 2015-2016 in the Ophthalmology Clinic of “Sf. Spiridon” County Clinical Emergency Hospital from Iasi. We included 87 eyes, from 87 patients, distributed in 4 groups: 24 patients - the control group (cataract), 26 patients - the type II diabetes group, 16 patients – POAG group, 21 patients - the combined disease group (POAG + diabetes). We recorded data related to the age of the patients (years), best corrected visual acuity (BCVA), intraocular pressure (IOP-mmHg), perimetry parameters (MD, PSD-dB), biometric parameters (axial lengths, anterior chamber depth, CDE - Cumulative Dissipated Energy, lens thickness). The duration of glaucoma/diabetes, the type and number of glaucoma medications were noted. Similarly, the duration of diabetes mellitus, glycemic value and glycosylated hemoglobin were recorded. Results: Mean age calculated for the control group was 72.33+/-11.26 years, 69.04+/-9.46 years for the DM group, 75.69+/-5.54 years for the POAG group and 59.95+/-3.89 years for the combined pathology. Secondly, we found the highest IOP in the POAG+DM group, compared with the rest of the study categories (20.33+/-2.3 mmHg in group IV vs. 18.19+/-4.3 mmHg in group III vs. 15.50+/-1.9 mmHg vs. 14.21+/-2.68 mmHg in group I), p<0.05. We found statistically significant differences between the four groups in respect of lens size and the CDE mean values. Our data revealed that the smallest energy was used in group IV (CDE=8.5+/-1.77), compared to all the other categories: I (CDE=17.79+/-7.36, p = 0.000), II (CDE=18.15+/-11.74, p = 0.000), III (CDE=13.90+/-8.11, p = 0.000). Estimated lens volume in group IV was 4.85+/-0.17mm in POAG+DM patients, significantly larger than the rest of the groups (p<0.05) Conclusions: younger age, higher IOP, larger lens volume and lower CDE mean values were the parameters significantly different in POAG patients, if diabetes was associated. Keywords: PRIMARY OPEN ANGLE GLAUCOMA, BIOMETRY, DIABETES

Glaucma and diabetes (DM) represent one of the most frequent causes of blindness worldwide. In USA by 2020, 3.3 million patients will develop glaucoma and up to 45% of diabetic patients will develop a form of retinopathy (1). Globally, WHO
estimates a total of 360 million cases of diabetes by 2030, whereas the incidence of glaucoma will also increase. Different sources point out that in 2013 there will be about 64.3 million glaucoma patients (2), increasing to 76 million in 2020 and to 111.8 million in 2040 (3). In addition, ocular damage to diabetes is the main cause of blindness in the active population (30-69 years). Recent epidemiological studies have shown that between 1990 and 2012 there was a 27% increase in the proportion of diabetes mellitus and over 64% in diabetic retinopathy cases (4). If the diagnostic features for the primary open angle glaucoma (POAG) definition are rather clear, the pathogenesis is still incompletely elucidated.

Several risk factors involved in the development and progression of POAG have been described, but the precise contribution of each one cannot be established. The general clinical context integrates glaucomatous illness into a systemic disease category (same as diabetes), based on the principle of “a suffering eye in a suffering body” (5).

Multiple risk factors impacting over DM also influence POAG. For example, lack of exercise in aerobic conditions or obesity may influence the evolution of diabetes or IOP, hence the risk of POAG (6, 7). Theoretically, between glaucoma and diabetes, there are several common pathogenic pathways related to pressure disorders (intraocular pressure, ocular perfusion pressure), microvascular disorders and neuroinflammation. From the clinical point of view, the relationship between POAG and DM triggers 2 coordinates as following: first, presence of diabetes mellitus increases the risk of POAG development and second, in a patient with POAG, the presence of DM enhances early changes with potential neurodegenerative effect.

As such the aim of our study was to emphasize the clinical changes and biometric alterations at baseline in primary open angle glaucoma (POAG) patients, if diabetes was associated.

MATERIAL AND METHODS

The study was designed in a cross-sectional manner, between 2015-2016 in the Ophthalmology Clinic of “Sf. Spiridon” County Clinical Emergency Hospital from Iasi. We included 87 eyes, from 87 patients with indication for cataract surgery, distributed in 4 groups: 24 patients - the control group (cataract), 26 patients - the type II diabetes group, 16 patients - POAG group, 21 patients - the combined disease group (POAG +diabetes). We recorded data related to the age of the patients (years), best corrected visual acuity (BCVA), intraocular pressure (IOP-mmHg), MD (dB) and PSD (dB) in automated perimetry (24-4 program, Sita Fast, Humphrey® Visual Field Analyzer, Carl Zeiss, Meditech, CA), biometric parameters: axial lengths, anterior chamber depth, lens thickness and CDE (Cumulative Dissipated Energy) during phacoemulsification. The duration of glaucoma/diabetes, the type and number of glaucoma medications were noted. Similarly, the duration of diabetes mellitus, glycemic value and glycosylated hemoglobin were recorded.

In the study, we only included cases of uncomplicated cataract surgery. Diagnosis of POAG was based on the EGS criteria, described somewhere else (8), whereas the diagnosis of diabetes was based on patients charts and previous documents. Patients with significant general or ophthalmological disorders (e.g. age-related macular
Clinical changes and biometric differences in patients with primary open angle glaucoma and diabetes

degeneration, retinal vascular occlusions) were excluded, as well as all the cases with previous ocular surgeries.

Cataract surgery was indicated by the ophthalmologist at a time when there was significant lens opacification or when the patient requested it due to significant alterations in the quality of life and vision. Biometric parameters were recorded via immersion A-scan technique.

**Ethics.** All patients enrolled in the study included in the doctoral research expressed verbally and in writing an agreement for participation in the study, by signing an informed consent. The study protocol and the informed consent were approved by the Ethics Commission of the “Grigore T. Popa” University of Medicine and Pharmacy Iasi, as well as by the similar department attached to the “Sf. Spiridon” County Clinical Emergency Hospital Iasi.

**Statistical analysis.** Data analysis was performed using the SPSS 20.0 software. The demographic data of the four groups were analyzed. Descriptive statistics elements were used to calculate the averages and median of all numerical parameters entered in the database (age, IOP, biometry parameters, duration of glaucoma/diabetes, number of topical medications in glaucoma, MD, PSD, CDE); p <0.05 was considered statistically significant. The correlations between the variables were performed by Pearson correlation test. The correlation coefficient (r) was declared significant for a p <0.05 value.

**RESULTS**

In the current study we evaluated data from 87 patients: 44 males (50.5%) and 43 females (49.5%). Yet the gender distribution within the study groups showed that in glaucoma patients there were more males (group III and IV), compared to healthy controls or diabetes group where females were more numerous (fig. 1).

![Fig. 1. Sex distribution between study groups](image)

Mean age of the subjects was 72.33 +/- 11.26 year in the control group, 69.04 +/- 9.46 years for the DM group, 75.69 +/- 5.54 years for the POAG group and 59.95 +/- 3.89 years in the combined pathology (fig. 2). Absolute values show that the oldest patients belong to the POAG group, whereas the youngest age was calculated for the subjects with combined pathology (POAG + diabetes). Differences were statistically significant when compared DM vs. POAG group (p=0.015), Control vs. POAG+DM group (p=0.000), DM vs. POAG+DM group (p=0.000), POAG vs. POAG+DM group (p=0.000).

The IOP dynamics between the four groups followed an opposite profile compared to age distribution (fig. 2). Thus, we found the highest IOP in the POAG+DM group, compared with the rest of the study categories (20.33 +/- 2.3 mmHg in group IV vs. 18.19 +/- 4.3 mmHg in group III vs. 15.50 +/- 1.9 mmHg in group II vs. 14.21 +/- 2.68 mmHg in group I), p<0.05.

The number of substances required for IOP control in the two groups with glaucoma did not show significant differences: 3 +/- 0.87 vs. 2.85 +/- 1.02 drugs (POAG vs. control).
POAG+DM, p=0.489). Yet the clinical impact of this finding might be different: if diabetes was associated with POAG, the patients had significantly higher IOPs despite similar, maximal treatment. Escalation of treatment (cataract surgery) in these glaucoma patients was necessary, at a younger age and longer life span compared to subjects with glaucoma, but without diabetes.

**Fig. 1.** Age of subjects compared between groups

**Fig. 2.** IOP means compared between groups

Biometric data was summarized in Table I. There were significant differences in these parameters regarding lens size and CDE mean value. Thus, the smallest amount of ultrasound energy was necessary in the POAG+DM group, when compared to the other study group categories. Differences in CDE values for the compared groups were: I vs. IV (p=0.000), II vs. IV (p=0.000), III vs. IV (p=0.000). Also, the largest lens was found in group IV, if diabetes was present in glaucoma patients (p<0.05 compared to healthy controls or POAG patients). No differences were present between the four groups regarding axial lengths (mm) or ACD (mm).
Clinical changes and biometric differences in patients with primary open angle glaucoma and diabetes

TABLE I
Comparison of means in biometric data between study groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>Diabetes mellitus group</th>
<th>POAG group</th>
<th>POAG+DM group</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL (mm)</td>
<td>22.87 +/- 0.64</td>
<td>22.97 +/- 0.40</td>
<td>22.74 +/- 0.66</td>
<td>22.87 +/- 0.65</td>
</tr>
<tr>
<td>ACD (mm)</td>
<td>2.96 +/- 0.41</td>
<td>2.81 +/- 0.31</td>
<td>2.80 +/- 0.54</td>
<td>2.74 +/- 0.31</td>
</tr>
<tr>
<td>L (mm)</td>
<td>2.36 +/- 0.35</td>
<td>4.12 +/- 0.26</td>
<td>3.79 +/- 0.63</td>
<td>4.85 +/- 0.17</td>
</tr>
<tr>
<td>CDE (mm)</td>
<td>17.79 +/- 7.36</td>
<td>18.15 +/- 11.74</td>
<td>13.90 +/- 8.11</td>
<td>8.5 +/- 1.77</td>
</tr>
</tbody>
</table>

AL – axial lengths; ACD - anterior chamber depth, L – lens, CDE – Cumulative Dissipated Energy

Clinical implication of this result proves that the structure of the lens in the glaucoma patients is different if diabetes is present; moreover, cataract surgery becomes necessary in younger ages and dictated also by a significantly higher IOP under maximally topical tolerated medication and increased lens size.

From functional deficit point of view, in this study the MD values were similar between groups and helped us categorize our glaucoma patients as having an “advanced disease”, according to the EGS criteria (tab. II). However, it should also be considered that the MD recordings might have been influenced by the degree of lens opacification (cataract), mostly since there was no concordance with the degree of localized glaucoma damage (PSD).

Separate analysis of PSD in our glaucoma patients showed that in the combined pathology (POAG+DM) group, the localized deficit was less prominent in comparison with the POAG group. Age has been shown to be a risk factor in POAG, therefore the significantly younger age of the POAG+DM group compared to POAG group might be an actual explanation for this finding. Duration of glaucoma between groups III and IV was similar (45.63 +/- 26.48 months vs. 36.86 +/- 15.86 months, p>0.05).

TABLE II
Functional perimetric parameters compared between glaucoma groups in the study

<table>
<thead>
<tr>
<th>Group</th>
<th>POAG group</th>
<th>POAG+DM group</th>
<th>p&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD (dB)</td>
<td>-13.59 +/- 9.35</td>
<td>-12.13 +/- 8.9</td>
<td>p=0.683</td>
</tr>
<tr>
<td>PSD (dB)</td>
<td>4.25 +/- 4.22</td>
<td>2.05 +/- 0.90</td>
<td>p=0.026</td>
</tr>
</tbody>
</table>

From the metabolic point of view, both groups of diabetic patients exhibited similar values of the blood sugar level: 171 mg/dL in group II vs. 155.05 mg/dL in group IV, p> 0.05. Yet a significant longer duration of diabetes was found in group II compared to group IV (133 +/- 77.82 vs. 115 +/- 81.24 months, p = 0.004), combined also with a poorer long term metabolic control. HbA1c mean values (%): 8.12 +/- 1.81 (group II) vs. 7.12 +/- 1.35 (group IV), p = 0.036.

In POAG and diabetes patients, clinical correlations relevant for this study were depicted in Table III.

PSD is correlated negatively with the age, therefore an earlier glaucoma deficit in younger patients, if diabetes is also present in POAG patients. An increase in medication was correlated with a decrease of the MD levels, stating that we treated more aggressively the patients once we observed a decrease in the functional perimetric parameters.
levels. No correlation was detected between the perimetric indices, as they might have not necessarily reflected the reality in terms of glaucoma severity, but lens opacification degree (MD is influenced by the opacities in the lens, as opposed to PSD).

Mean IOP is correlated with the intensity of treatment (number of topical medications) and the blood sugar level. Therefore, if diabetes is associated with POAG, it induces an increase in IOP, increasing the demand for an aggressive treatment.

In POAG, clinical correlations relevant for this study were depicted in Table IV.

TABLE III
Correlations between clinical parameters in POAG+DM patients

<table>
<thead>
<tr>
<th>Pearson test (r)</th>
<th>Age</th>
<th>IOP</th>
<th>Number of medications</th>
<th>MD</th>
<th>PSD</th>
<th>Blood sugar</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>p&lt;0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>-0.148</td>
<td>0.09</td>
<td>0.322</td>
<td>-0.461</td>
<td>-0.195</td>
<td>-0.112</td>
</tr>
<tr>
<td></td>
<td>0.521</td>
<td>0.529</td>
<td>0.14</td>
<td>0.307</td>
<td>0.287</td>
<td>0.520</td>
<td>0.140</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.681</td>
<td>0.529</td>
<td>0.14</td>
<td>0.231</td>
<td>0.208</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.207</td>
<td>0.024</td>
<td>1</td>
<td>0.024</td>
<td>0.929</td>
<td>0.135</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.322</td>
<td>-0.545</td>
<td>0.168</td>
<td>-0.350</td>
<td>0.076</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.061</td>
<td>0.287</td>
<td>0.168</td>
<td>0.396</td>
<td>0.561</td>
<td>0.428</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.039</td>
<td>0.135</td>
<td>0.195</td>
<td>0.396</td>
<td>0.614</td>
<td>0.114</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.036</td>
<td>0.016</td>
<td>0.195</td>
<td>0.396</td>
<td>0.557</td>
<td>0.057</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.630</td>
<td>0.428</td>
<td>0.355</td>
<td>0.396</td>
<td>0.614</td>
<td>0.114</td>
</tr>
</tbody>
</table>

TABLE IV
Correlations between clinical parameters in POAG patients

<table>
<thead>
<tr>
<th>Pearson test (r)</th>
<th>Age</th>
<th>IOP</th>
<th>Number of medications</th>
<th>MD</th>
<th>PSD</th>
<th>Blood sugar</th>
</tr>
</thead>
<tbody>
<tr>
<td>p&lt;0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>0.154</td>
<td>0.338</td>
<td>-0.533</td>
<td>-0.01</td>
<td>-0.133</td>
</tr>
<tr>
<td></td>
<td>0.569</td>
<td>0.889</td>
<td>0.089</td>
<td>0.091</td>
<td>0.970</td>
<td>0.624</td>
</tr>
<tr>
<td></td>
<td>0.038</td>
<td>0.790</td>
<td>0.790</td>
<td>0.042</td>
<td>0.807</td>
<td>0.513</td>
</tr>
<tr>
<td></td>
<td>0.889</td>
<td>0.042</td>
<td>1</td>
<td>0.503</td>
<td>0.311</td>
<td>0.521</td>
</tr>
<tr>
<td></td>
<td>0.091</td>
<td>0.807</td>
<td>0.115</td>
<td>0.115</td>
<td>0.024</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td>0.513</td>
<td>0.311</td>
<td>0.649</td>
<td>0.031</td>
<td>0.427</td>
</tr>
<tr>
<td></td>
<td>0.970</td>
<td>0.042</td>
<td>0.024</td>
<td>0.031</td>
<td>0.031</td>
<td>0.191</td>
</tr>
<tr>
<td></td>
<td>0.624</td>
<td>0.030</td>
<td>0.039</td>
<td>0.191</td>
<td>0.082</td>
<td>0.082</td>
</tr>
</tbody>
</table>

IOP levels in these patients correlates positively with the functional localized deficit (PSD) and with the increase of blood sugar levels (although we were not analyzing patients with diabetes). Of course, the higher the IOP became in these
Clinical changes and biometric differences in patients with primary open angle glaucoma and diabetes

patients, the more aggressive the treatment became. In this study category, we obtained a correlation between the perimetric indices (MD/ PSD) which might indirectly state that based on older age and lack of a metabolic disorder such as diabetes, the MD was less influenced by the lens compound contributing to the general reduced retinal sensitivity (cataract formation) and the glaucoma disease evolved in its specific correlated pattern.

DISCUSSION

In this study, the presence of diabetes modified the clinical and functional parameters, all together with some phacoemulsification parameters (CDE) in glaucoma patients. Biometric measurements were similar between groups, except for the mean lens thickness (mm) that was increased in the combined pathology group, compared to the other categories of interest (controls or glaucoma patients). This only proves that the presence of diabetes induces an early and excessive hydration of the collagen lamellas, based on some very low levels of sorbitol in adult diabetic lenses. The altered osmotic mechanism increases the risk of cataract even more, altogether with glycation and oxidative stress (11). The relationship between the polyol pathway and sugar cataracts has been studied extensively using streptozotocin-induced diabetic rats and galactose fed rats as animal models for insulin-dependent diabetes mellitus (IDDM). In these models, sugar cataracts progress (12).

Our study proves that the metabolic disorders are more frequent in younger female patients, while in older male patients’ glaucoma is more frequent. A higher mean IOP at presentation, combined with younger age and increased lens volume required prompt cataract surgery intervention in the combined group. Aim of our approach was to decrease IOP and reduce the number of topical medications, therefore an improvement quality of life in our POAG patients. It is true that in both glaucoma groups, the number of topical substances was maximal and comparable, yet the mean IOP was significantly higher in the POAG+diabetes group. Therefore, a supplementary metabolic disorder may alter the overall status in glaucoma patients.

An IOP in its high teens (18 mmHg, as we calculated in our study) in a moderate-advanced glaucoma patient increases the risk of POAG progression; therefore, a surgical intervention was discussed. In the context of glaucoma patients, cataract extraction decreases IOP and/or lowers the number of substances used to control IOP (13). Moreover, cataract extraction before trabeculectomy offers a safer approach both for the patient and the surgeon if performed first (13). As such we preferred this approach in our study. Adding a fourth substance would have been an option if the stage of the glaucoma was different (early) and if the quality of life in our patients had remained the same.

Using the lowest ultrasound energy in the combined pathology group pleads only for the above-mentioned changes induced by metabolic imbalances in the lens, if diabetes is discussed. Therefore, a different structure and density is met in the diabetic lens compared to the normal involutional changes induced by age alone. The lens capsule is impermeable, therefore an increase in the oncotic pressure within the lens accelerates cataract formation. Intense hydration of collagen lamellas produces soft intumescence of the lens in diabetic cataract compared to sclerotic changes in
age related cataract.

Functional parameters in glaucoma patients are also influenced by diabetes. Based on the Hodapp classification, our POAG cases are categorized as moderate to advanced disease, but formation of cataract can artificially decrease MD values and influence glaucoma severity scale. In this respect, by inspecting the PSD maps the clinician might interpret the parameters in a different way as it was the case in our study. The discrepancy between the MD/PSD maps pleaded also for a cataract influence over the parameters than only glaucoma damage. An interesting aspect that we found in our study was that the mean PSD values in the combined pathology (POAG+diabetes) group were decreased compared to the POAG group. A possible explanation for less localized damage in the POAG+diabetes category could be the age aspect: age glaucoma damage increases with age; therefore, an older age might have more pronounced damage (POAG group, mean age=75 years old) compared to younger age (POAG+diabetes group, mean age = 59 years-old). Still it is difficult to establish the exact glaucoma extension of damage in both groups, since patients from both categories were evaluated before cataract surgery, for which there was a strong recommendation.

Study limitations were the small number of patients and the echo-biometric methods for the anterior segment measurements.

CONCLUSIONS

In our study we found several clinical changes that “modulated” the decision about the best treatment options in primary open angle glaucoma patients, especially if they associated a general risk factor such as diabetes. Further studies and more data, especially using recent advances in ocular imaging such as AS-OCT technology, are needed to provide a complete overview of anterior segment measurements, so as the best management is offered to diabetic glaucomatous patients.

REFERENCES

Clinical changes and biometric differences in patients with primary open angle glaucoma and diabetes

10. Fingeret M. Optometric Clinical Practice Guideline, care of Patient with Open Angle Glaucoma, American Optometric Association 2011

THE BENEFITS OF SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS ON METABOLIC PARAMETERS

Sodium-glucose cotransporter 2 inhibitor (SGLT2i) blocks reabsorption of glucose by inhibiting SGLT2 in kidney, promotes the renal excretion of glucose and improves blood glucose control without requiring insulin secretion. A recent study retrospectively picked up patients with type 2 diabetes who had been continuously prescribed SGLT2i for 3 months or more (26 patients treated with tofogliflozin, 34 patients with canagliflozin, 27 patients with empagliflozin, 23 patients with ipragliflozin, 68 patients with dapagliflozin and 71 patients with luseogliflozin) and compared metabolic parameters including coronary risk factors before the SGLT2i treatment with the data at 3 and 6 months after the SGLT2i treatment started. Each SGLT2i ameliorated metabolic parameters, in different patterns. SGLT2is reduced body weight, systolic and diastolic blood pressures, plasma glucose, hemoglobin A1c, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, uric acid, triglyceride and non-high-density lipoprotein-cholesterol (HDL-C), and elevated HDL-C; however, they did not affect LDL cholesterol levels. Change in each metabolic parameter was significantly correlated with each metabolic parameter at baseline (Yanai H, Hakoshima M, Adachi H, Kawaguchi A, Waragai Y, Harigae T, Masui Y, Kakuta K, Hamasaki H, Katsuyama H, Kaga T, Sako A, Effects of Six Kinds of Sodium-Glucose Cotransporter 2 Inhibitors on Metabolic Parameters, and Summarized Effect and Its Correlations with Baseline Data. J Clin Med Res 2017; 9(7): 605-612. doi: 10.14740/jocmr3046w. Epub 2017 May 22).

Dan Lupaşcu