GLAUCOMA EVOLUTION IN PATIENTS WITH DIABETES

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GLAUCOMA EVOLUTION IN PATIENTS WITH DIABETES (Abstract): Glaucoma and diabetes are two chronic diseases with a long suspected pathogenic relationship. **Purpose:** Screening for glaucoma in patients with diabetes. **Material and methods:** A retrospective study on 92 eyes from 46 patients with primitive open angle glaucoma (POAG) (normal and hypertensive) and intraocular hypertension (OHT) receiving medication and / or surgery associated with diabetes mellitus (DM) (type I, type II, mixed) is presented. Participants were divided into two groups as following: 16 eyes with glaucoma and diabetic retinopathy changes (group1) and 76 eyes with glaucoma and without diabetic retinopathy changes (group 2). The following parameters were analysed: ocular pressure (Goldmann applanationometry), perimeter development (computerized perimetry) and fundus condition (absence, presence or progression of diabetic retinopathy). **Results:** In patients with glaucoma and diabetic retinopathy (8 patients) we found a mean difference between treated intraocular pressure (IOP) and IOP last untreated control of 4.95 mmHg; a depreciation of the MD by 4.18 dB and an average number of glaucoma medications used of 0.889 ± 1.054. Predominant changes in proliferative diabetic retinopathy were mild. In patients with glaucoma in the absence of diabetic retinopathy, the average difference between untreated IOP and IOP under treatment at the last check-up was 1.63 mmHg, the MD depreciation was by 0.65 dB and the average number of glaucoma medications used was 0.795 ± 0.978. **Conclusions:** No statistically significant differences in terms of initial and final pressure were found. No statistically significant differences in the evolution of changes in perimeter between the two groups were observed. The presence of non-proliferating diabetic retinopathy influenced (only marginally statistically) the glaucomatous disease progression. Large comparative prospective studies are needed for the long-term follow up. **Keywords:** POAG, DIABETES, PIO, MEAN DEVIATION, DIABETIC RETINOPATHY

Glaucoma and diabetes are two chronic diseases that affect the population for over 40 years, views on its relationship are considered pathogenic (1). Numerous studies have attempted to find an association between diabetes and primary open-angle glaucoma (POAG), some successfully, some not. MO Gordon and colleagues presented a study of 1637 subjects in 1999, which included a large number of risk factors including diabetes. The study concluded that 3.1% of the population does develop glaucoma, and that diabetes acts as a protective factor to decrease the probability of developing POAG (2). This early conclusion was in part due to a relatively small
The number of people with diabetes excluding those with diabetic retinopathy changes. Several studies have tried and have failed to demonstrate an association between diabetes and glaucoma. In an article by Benkes (3) in 1967 suggested for the first time the relationship between glaucoma and diabetes, "diabetes occurs more frequently in those with POAG than in the population without glaucoma claiming, glaucoma is more prevalent in patients with diabetes than without". The Rotherham Study concluded, "newly diagnosed diabetes and high blood glucose levels are associated with elevated IOP and glaucoma with high pressure" (4). In a recently published article entitled "Diabetes - risk factor for glaucoma?", the authors showed that both diseases have a vascular component and retrobulbar blood flow abnormalities in retinal microcirculation were found in both diabetes and glaucoma (5). Our study objective was to follow the development of glaucoma specifically in patients with diabetes.

MATERIAL AND METHODS

We performed a retrospective study on 92 eyes from 46 patients recorded with normal or hypertensive POAG, an OHT treated with drugs and/or surgery both associated with diabetes (type I, II and mixed). All patients were selected from „Sf. Spiridon” University Hospital of Iasi between January 2009 – May 2012. The inclusion criteria were: normal or hypertensive glaucoma, OHT associated with diabetes (type I, II and mixed). Patients with other types of glaucoma were excluded (pseudoexfoliation, pigment, cortisone, and primitive neovascular angle closure) as well as those without associated diabetes. Participants were divided into two groups as following: group 1 represented by patients with glaucoma and changes of diabetic retinopathy (DR) and group 2 patients with glaucoma and without DR.

All patients were monitored under the following parameters: the clearance pressure (with Goldmann applanotonometer), the perimetrical progression (by automated perimetry with Humphrey Field Analyzer II) and fundus change evaluated with the Volk lens 78D (absence, presence and progression of DR). It was also recorded the duration of glaucoma, diabetes and number of glaucoma medications used.

Diagnosis criteria for normal or hypertensive POAG were: age >35 years, normal IOP or >21mmHg without treatment, open angle gonioscopy, the presence of optic nerve damage (ratio c/d > 0.5), abnormal visual field (Humphrey Field Analyzer by perimetry) and normal or diffuse or localized defects in the retinal nerve fiber layer (optical Coherence tomography Cirrus HD-OCT Zeiss) (6).

Evaluations of the changes in diabetic retinopathy were performed with Volk lens and retinal photography with Fundus Camera Zeiss. Retinal changes in dilated pupils were monitored. The criteria for classification as DR changes (ETDRS) were the following: unchanged or absence of signs of DR, mild nonproliferative diabetic retinopathy (presence of only microaneurysms), moderate DR (microaneurysms, haemorrhages in 2-3 quadrants, venous dilatation and exudates), severe DR (microaneurysms, hemorrhages in all quadrants, dilated veins in 2-3 quadrants, exudates) and proliferative diabetic retinopathy (neovascularization disk and retina in different quadrants). It was considered progression of DR any new clinical item appearing on subsequent checks that led to their classification as severe nonproliferative or proliferative diabetic retinopathy (7). Sigma Plot was used for the statistical analysis of the results (student t test).
RESULTS

In our study all the 92 eyes from 46 patients met the eligibility criteria. The mean age was 62.87 ± 8.4 years (between 39 and 80 years old). Among patients with DM 36 had DM type II, 5 had DM type I and 5 with insulin-dependent DM type II. From all studied eyes, 72 eyes (78.26%) had POAG, 10 eyes (10.87%) had normal tension glaucoma (NTG) and 10 eyes (10.87%) OHT (fig.1). Regarding the changes in diabetic retinopathy, of the 8 patients, 5 had mild changes in diabetic retinopathy (15%), 3 had proliferative diabetic retinopathy (7%) and the rest (78%) did not show any change (fig.2).

![Fig. 1. Distribution of patients with glaucoma POAG = primitive open angle glaucoma, OHT = ocular hypertension, NTG = normal tension glaucoma](image1)

![Fig. 2. Distribution changes of diabetic retinopathy NPDR = diabetic retinopathy mild form, PDR = proliferative diabetic retinopathy, Without DR = no modification of diabetic retinopathy](image2)

The average duration in years of glaucoma in group 1 was 1.7 ± 1.16 (range 0-3) and 4.33 ± 4.602 (range 0-19) in group 2.

No statistically significant differences were found between the two groups (P <0.05 for significant relevant statistics) (tab. I).

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Glaucoma duration (years)</th>
<th>t student</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP 1</td>
<td>1.7 ± 1.16 (0-3)</td>
<td>(P=0.818)</td>
</tr>
<tr>
<td>GROUP 2</td>
<td>4.33 ± 4.602 (0-19)</td>
<td></td>
</tr>
</tbody>
</table>

The average duration of diabetes in years was in group 1 with 9 ± 10.029 (range 0-26) and 4.59 ± 4.284 (range 0-17) in group 2, no statistically significant differences existed between the two groups (tab. II).

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Diabetes duration (years)</th>
<th>t student</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP 1</td>
<td>9 ± 10.029 (0-26)</td>
<td>(P=0.081)</td>
</tr>
<tr>
<td>GROUP 2</td>
<td>4.59 ± 4.284 (0-17)</td>
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</table>
The mean number of glaucoma medications used was similar in the two groups, respectively 0.889 ± 1.054 (range 0-3) in group 1 (glaucoma + DR) and 0.795 ± 0.978 (range 0-3) in group 2 (glaucoma without DR) as there were no statistically significant differences in student t-test between the two groups (tab. III). In group 1 the glaucoma and DR average difference between the initial untreated IOP and the final treated IOP at the last check-up was 4.9 mmHg. Patients whose IOP was less than 23 mmHg after one single medication did not require any further intervention to reduce the IOP (fig. 3).

In group 2 (glaucoma and without DR) we found a mean difference of 1.63 mmHg between the initial untreated IOP and final treated IOP at the last check-up. The initial pressure was also lower compared to the group 1. As a consequence the majority of cases did require a small number of drugs and only 2 cases with IOP >30 mmHg required three drugs to reduce pressure (fig. 4).

By comparing the mean IOP of the two groups using Student t test a p value of 0.062 was obtained. This value is however statistically insignificant since p <0.05 is considered statistically significant (fig. 5).

Analyzing the characteristic parameters of standard perimeters, particularly of Mean Deviation (MD) an impairment of the MD's of 4.18 dB was found in group 1 (glaucoma and DR) (fig. 6). In group 2 (glaucoma and without DR) a MD's depreciation of 0.65 db was found (fig. 7).

**TABLE III.**

<table>
<thead>
<tr>
<th></th>
<th>group1</th>
<th>group2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean no. of glaucoma medications</td>
<td>0.889 ± 1.054 (0-3)</td>
<td>0.795 ± 0.978 (0-3)</td>
</tr>
<tr>
<td>T student</td>
<td>(p=0.847)</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 3.** Statistical description of the mean pressure difference outcomes in group 1

Pf = final pressure therapy, pi = initial pressure therapy,

DP_mean = average difference between the final and initial pressure
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**Fig. 4.** Statistical description of the mean pressure difference outcomes in group 2

\[ \text{DP}_\text{mean group 2} = \text{P}_f - \text{P}_i = -1.63 \]

\( \text{P}_f = \text{final pressure therapy, } \text{P}_i = \text{initial pressure therapy,} \)

\( \text{DP}_\text{mean} = \text{average difference between the final and initial pressure} \)

**Fig. 5.** Statistical significance average initial and final pressure between the two groups

**Fig. 6.** Statistical description of the results - MD mean value group 1

\( \text{MD}_f = \text{mean deviation final, } \text{MD}_i = \text{mean deviation initial from the first control} \)
However when comparing the average MD of the two groups using Student t test a p-value = 0.044 was obtained which is a statistically significant value although only marginal (p<0.05 to be statistically significant) (fig.8). The statistical analysis of the data showed higher initial value of the IOP in the group 1 (glaucoma+DR), which required a greater number of drugs to reduce it, while long standing diabetes (0-28 years) correlated positively with the presence of diabetic retinopathy and the MD's important depreciation (4.18 db) vs group 2 (glaucoma and without modifications RD). All these results reveal the statistically significant difference in terms of the average MD and confirm that this influenced the diabetic retinopathy (although marginally statistically) and the glaucomatous disease progression.

DISCUSSION
Secondary conditions such as vascular degeneration related to diabetes cause some severe risks to the eye such as diabetic retinopathy, crystalline opacities, increased intraocular pressure, rubeosis iridis and open-angle glaucoma. Furthermore IOP has a role in the development of diabetic reti-
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nopathy and influences the development progression of glaucoma. Eyes with proliferative diabetic retinopathy had IOP lower than those with non-proliferative diabetic retinopathy. Increased IOP may protect by delaying DR changes. The statement "Increased IOP may protect by delaying DR changes" is controversial; low IOP associated with worsening diabetes as a logical consequence of the Starling law (on the balance between the intravascular and extravascular fluid transfer) (8). Many studies on patients with glaucoma and diabetes are clinical and retrospective and population-based. However obtaining sufficient information from any systematic retrospective study is difficult. A large number of studies have been conducted over time, some have found an association between glaucoma and diabetes, others have shown the opposite (2), or failed (Baltimore Eye Survey, The Rotherham Study) (9, 10, 11). The controversial Ocular Hypertension Treatment Study conducted in 2002 (2) does not find a correlation between the two disorders further supporting that diabetes is a protective factor for glaucoma (glaucoma develops only 3.1% of those with diabetes). It should be noted that compared to our study they did not include patients with diabetic retinopathy, which could change the results of the study. The 22% of those included in our study with diabetic retinopathy, glaucoma influenced the evolution (depreciation MD's with 4.91 dB 0.65 dB in group 1 vs group 2) even if marginal (p = 0.044, p < 0.05 to be statistically significant). The age group 1 diabetes in years (range 0 - 29 years old) also may play a role in the changes of diabetic retinopathy and glaucomatous disease evolution. Of those that have found an association between the two disorders are groups for which their group resembles the selection of cases and results of our study (10, 11, 12). Barbara Klein and colleagues published in BJO 1997 a prospective study at 10-year in which she examined the incidence of glaucoma in patients with DM. In her study she found that glaucoma is more prevalent in those with long-term diabetes and treated with insulin (12). Los Angeles Latino Eyes Study, a population-based study that included patients with glaucoma DM type II and demonstrated that this DM type II and its long-evolution (duration > 15 years) had a higher prevalence (40%) of developing glaucoma (p<0.0001) (13). The difference from our study is that it included only patients with type II diabetes (a < 30 years treated with oral agents or by diet) while diagnosis of glaucoma was based on the optic nerve appearance, regardless of the IOP. We found that in our group, most participants had DM type II (78%), a small percentage being with DM type I and mixed. Similar Blue Mountain Study, study of the population range that includes 40% black participants, argues that there is a significant and consistent association between diabetes and glaucoma (14).

Despite all the contradictions in the literature, our study shows similar results to recent studies, however we believe a prospective, general study on a larger number of patients and with a longer follow-up period should be conducted.

CONCLUSIONS

This study demonstrated an association and support that diabetes influences the evolution of the open-angle glaucoma in our patients. We have also found statistically significant differences in the evolution perimeter changes (Mean Deviation) between the two groups (p = 0.044). In group
1 represented by patients with glaucoma and diabetic retinopathy depreciation, MD was 4.91 dB (glaucoma progression) compared with group 2 (glaucoma + without RD) which was only 0.65, this allowed us to say that the presence of diabetic retinopathy changes even if statistically marginal influenced by the evolution of glaucomatous disease. Regarding the evolution of initial and final IOP no statistically significant differences between the two groups were found. This study has however several limitations: it is a retrospective study, the number of patients is small, high group heterogeneity (smaller number of patients with glaucoma and RD) and short duration of follow-up. Future prospective studies containing comparative larger batches of patients are necessary for a more accurate idea of the influences of the two diseases.

REFERENCES