

Diabete et Primary Open-Angle Glaucoma: Comparison of RNFL Progression and Ganglion Cell Loss in Diabetic and Non-diabetic Primary Open-Angle Glaucoma Patients

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Abstract: Primary open-angle glaucoma is a progressive chronic optic neuropathy, typically bilateral, that occurs after the age of 40 years. It is the second leading cause of irreversible blindness in the world. Primary open-angle glaucoma corresponds to a progressive loss of retinal ganglion cell characterized by an excavation of the optic disc associated with typical visual field defects. Objective of the study: To evaluate the impact of diabetes on the evolution of RNFL thickness and ganglion cell layer in patients followed for primary open-angle glaucoma. Materials and methods: Our 4-year retrospective study between 2017 and 2021 included 80 patients (160 eyes) with primary open-angle glaucoma divided into 2 comparable groups: the 1st group patients primary open-angle glaucoma without type 2 diabetes mellitus (DM-) and the 2nd group patients primary open-angle glaucoma with type 2 diabetes mellitus (DM+). Results: The average age was 59 years for the 1st group and 62 years for the 2nd group, the sex ratio was 1.2 for the 1st group and 1 for the 2nd group, an average follow-up between 3 and 4 years. Concerning the RNFL, the loss for the diabetic group was $-3.33\mu\text{m}/\text{year}$ and significantly slower than that in the group with glaucoma alone which was $3.8\mu\text{m}/\text{year}$ with a p less than 0.001. For ganglion cells, the loss for the diabetic group was $3.2\mu\text{m}/\text{year}$ is significantly faster than that in the group with glaucoma alone which was $-1.56\mu\text{m}/\text{year}$ with a p less than 0.001. Conclusion: Diabetes probably plays a confounding role in relation to RNFL prompting vigilance in the follow-up of primary open-angle glaucoma. A larger longitudinal study with a larger sample size is needed to accurately quantify the impact on RNFL.

Keywords: POAG, RNFL, Ganglion Cells, Diabetes, Loss

1. Introduction

Primary open-angle glaucoma (POAG) is a chronic progressive optic neuropathy corresponding to a loss of retinal ganglion cells and characterized by morphological changes of the optic nerve head (or papilla) associated with a typical visual field impairment [1]. GPAO is a bilateral

disease, occurring in adulthood, most often after the age of 40. Its pathophysiology is imperfectly known.

The identification of the risk factors of progression is essential to determine the therapeutic strategy and the frequency of follow-up. [2]

Among these risk factors, we find diabetes with two processes: elevation of intra ocular pressure and alteration of

vascular supply that enter the pathophysiology of POAG. [3, 4]

Objective of the study: to evaluate the impact of diabetes on the evolution of RNFL thickness and ganglion cell layer (CGL) in patients followed for primary open angle glaucoma.

2. Patients and Methods

A 4-year retrospective case-control study was established December 2017- December 2021 at the Ophthalmology Department of Cheikh Khalifa Ibn Zaid Hospital in Casablanca.

The material used is the 3D OCT, the statistical study was made by the SPSS version 20 software for the statistical study.

Our study was done on 100 patients (200 eyes) with POAG divided into 2 comparable groups: the 1st group POAG without diabetes (POAG /DM-) and the 2nd group POAG with diabetes (POAG /DM+).

Our inclusion criteria were: POAG beginners with MD < 4 dB, known type 2 diabetes, under treatment and well balanced (glycated hemoglobin HbA1c < 7%) and an average follow-up between 3 and 4 years.

Our exclusion criteria were advanced glaucoma, secondary glaucoma, proliferative diabetic retinopathy, macular edema, or retinal laser.

All our patients were monitored every six months with a complete ophthalmological examination: slit lamp examination, measurement of eye tone, fundus examination

with photographs of the optic nerve head. A visual field and OCT were performed at baseline and then every 6 months during follow-up. Diabetes monitoring was checked during each control.

Any diabetic retinopathy or other retinal disease that appeared during follow-up and was diagnosed either by fundus examination or OCT and any patient who received retinal laser treatment were excluded from our study.

3. Results

The mean age was 59 years for the 1st group and 62 years for the 2nd group.

The sex ratio was 1.2 for the 1st group and 1 for the 2nd group.

Concerning the RNFL, for the 1st group POAG /DM- (100 eyes); the average of global RNFL of the 100 eyes was 99, 75 Vs. 88, 35 μ m after 3 years of evolution and thus a loss of 11.4 μ m/3years and thus a loss of 3. 8 μ m/year with a standard deviation of 5.2 μ m while for the POAG /DM+ group the mean RNFL was 90.95 VS 100.97 μ m after 3 years of evolution with a loss of -10 μ m/3 years and thus a loss of -3.33 μ m/year and a standard deviation of 5.1 μ m. Thus, the loss of RNFL for the diabetic group which was -3.33 μ m/year is significantly slower than that in the group with glaucoma alone which was 3.8 μ m/year with a p less than 0.001.

| Group statistics | | | | |
|------------------|-----|---------|--------------------|---------------------|
| diab | N | Average | Standard deviation | Mean standard error |
| DIFFRNFL | 100 | 4,3750 | 5,29987 | ,83795 |
| 1,00 | 100 | -5,0500 | 5,11884 | ,80936 |

| Independent samples test | | | | | | | | | |
|--------------------------|---------------------------------|---|------|------------------------------|--------|-------------------|-----------------|---------------------------|---|
| | | Levene's test for equality of variances | | t-test for equality of means | | | | | |
| | | F | Sig. | t | ddl | Sig. (two-tailed) | Mean difference | Difference standard error | 95% confidence interval of the difference |
| DIFFRNFL | hypothesis of equal variances | ,022 | ,882 | 8,090 | 78 | ,000 | 9,42500 | 1,16500 | 7,10568 11,74434 |
| | hypothesis of unequal variances | | | 8,090 | 77,906 | ,000 | 9,42500 | 1,16500 | 7,10562 11,74438 |

Figure 1. Statistical study for the progression of the RNFL.

| Group statistics | | | | |
|------------------|-----|---------|--------------------|---------------------|
| diab | N | Average | Standard deviation | Mean standard error |
| DIFFCGL | 100 | -1,7250 | 3,23433 | ,51139 |
| 1,00 | 100 | 3,9000 | 6,79668 | 1,07465 |

| Independent samples test | | | | | | | | | |
|--------------------------|---------------------------------|---|------|------------------------------|--------|-------------------|-----------------|---------------------------|---|
| | | Levene's test for equality of variances | | t-test for equality of means | | | | | |
| | | F | Sig. | t | ddl | Sig. (two-tailed) | Mean difference | Difference standard error | 95% confidence interval of the difference |
| DIFFCGL | Hypothesis of equal variances | ,596 | ,442 | -4,726 | 78 | ,000 | -5,62500 | 1,19012 | -7,99435 -3,25565 |
| | Hypothesis of unequal variances | | | -4,726 | 55,802 | ,000 | -5,62500 | 1,19012 | -8,00929 -3,24071 |

Figure 2. Statistical study for the progression of the ganglion cells.

For the ganglion cells, in the POAG /DM- group the average ganglion cells of the 100 eyes was 100.5 Vs. 105.2 μm after 3 years of evolution and thus a loss of $-4.7\mu\text{m}/3$ years and thus a loss of $-1.56\mu\text{m}/\text{year}$ with a standard deviation of 3.2 while for the POAG /DM+ group the mean CG was 102.2 VS 92.6 μm after 3 years of evolution with a loss of $9.6\mu\text{m}/3\text{years}$ and thus a loss of $3.2\mu\text{m}/\text{year}$ and a standard deviation of 6.8 μm . Thus, the loss of LMC in the diabetic group, which was $3.2\mu\text{m}/\text{year}$, was significantly faster than that in the group with glaucoma alone, which was $-1.56\mu\text{m}/\text{year}$ with a p value of less than 0.001.

4. Discussion

Primary open angle glaucoma (POAG) is an anterior optic neuropathy of chronic and progressive course, characterized by perimeter alteration and excavation of the specific optic disc. [5] This neuropathy is usually accompanied by ocular hypertension. The iridocorneal angle remains open in gonioscopy.

Its pathophysiology is imperfectly known with 2 theories: mechanical compressive suggesting that ocular hypertonia (HTO) would lead to the loss of retinal nerve fibers by compression of the optic nerve head and the cribriform lamina [6], and vascular hypoxic suggesting that a circulatory insufficiency in the blood capillaries of the optic nerve head would lead to a lack of nutritional supply to the retinal ganglion cells and their axons. [7]

Its management has evolved with the development of structural imaging of the optic nerve in optical coherence tomography (OCT) with study of the RNFL and the CGL, and with the improvement of the follow-up of the visual field examinations thanks to automated tools of analysis of the progression.

In our study, eyes in the POAG/DM group showed slower RNFL thinning than those in the POAG/DM- group. In a hypertensive glaucoma model, blockade of vascular endothelial growth factor (VEGF) resulted in a significant increase in neuronal cell death. [8].

Thus, the suggested protective mechanisms against glaucomatous damage could be the overexpression of VEGF factor in the diabetic retina, [4] which could be a strategy to rescue and protect the retinal neurons. [9].

Several studies such as the Blue Mountains Study, the Los Angeles Latino Study and the Rotterdam Eye Study have found a significant association between glaucoma and diabetes.

However, the role of diabetes in GPAO is still controversial. The Ocular Hypertension Treatment Study (OHTS) concluded that diabetes protected patients with hypertension from developing or worsening glaucoma after 72 months of follow-up, [10]. In contrast, the Los Angeles Latino Eye Study, a cross-sectional study, found a higher prevalence of glaucoma in patients with diabetes (type 2) [11]. Conflicting results are given by four large multicenter randomized clinical trials [12-16]. This contradiction may be

due to diabetes itself; in none of these studies was the stage of diabetic retinopathy or other complications of diabetes studied.

The severity of glaucoma is also an influencing factor; thus, severe glaucoma gives variable results and cannot be followed by a visual field [17].

The visual field remains the most useful examination to detect functional loss of glaucoma but sometimes anatomical changes of the RNFL can be found despite the stability of the visual field [18]. Thus, studies have shown that the RNFL is thicker in POAG/DM patients than in POAG/DM- patients [19]. But also, diabetes protected against glaucomatous optic nerve damage [20]. Thus, the role of diabetes in glaucomatous progression is still a matter of debate.

In a study published in May 2018 in the American Journal of Ophthalmology, by Huiyuan Hou comparing the progression of RNFL in diabetic and non-diabetic POAG patients over 1 year of evolution on 197 eyes: 55 eyes of 32 POAG /DM+ and 142 eyes of 111 POAG /DM- showed the association of type 2 diabetes with RNFL thickness change based on uni-variate analysis thus, the mean rate of overall RNFL loss in the POAG / DM+ group was significantly slower ($-0.40\mu\text{m} / \text{year}$) compared to the POAG / DM- group ($-0.83\mu\text{m} / \text{year}$) with a P at 0, 01 which is consistent with our study which leads us to believe that the presence of diabetes can mask the loss of RNFL and is then a confounding factor that must be taken into account in the interpretation of OCT in the follow-up of POAG and this may be due to intra or extracellular edema, exudates, hemorrhage, fibrinous reaction surrounding the optic nerve head. [21]

Several hypotheses have been proposed to explain the association between DM and POAG. Neuronal stress secondary to hyperglycemia and chronic dyslipidemia [22], dysfunction of retinal vascular endothelial cells with loss of pericytes leading to blood flow dysregulation [23-25, 4], remodeling of the connective tissue of the optic nerve head as well as the trabeculum and lamina cribrosa; modification of the latter two lead to an increase in ocular tone and thus to an additional mechanical stress on the optic nerve head [24, 25]. In addition, disturbances in carbohydrate metabolism could also be responsible [26]. Thus, all the factors mentioned underline the importance of vascular risk factors in the pathogenesis of POAG.

Earlier meta-analyses suggested that diabetic patients are at a significantly increased risk of developing [27-29]. In a study by Zhao et al. the risk of glaucoma increased by 5% for each year since diabetes diagnosis; their pooled analysis presented a 0.18 mmHg difference between IOP in patients with diabetes, compared to those without diabetes [30]. Our study identified no significant relationship between the prevalence of POAG and diabetes mellitus; the high heterogeneity among studies and, thus, the conclusion, must be interpreted with caution. Results for case-control studies could be different, e.g., in a Korean study, diabetes was associated with POAG in all age groups (the HR was 1.2 for individuals aged 40–59 years, and 1.18 for those aged 60–79

years) [31]. However, it is known that case-control designs are potentially viable to selection bias [32].

For ganglion cells, several studies such as the study by Timothy S. Kern and Alistair J. Barber on neurodegenerative mechanisms have shown that there is an additional loss of ganglion cells caused by diabetes in glaucoma patients, which supports our study [33]. This loss is explained by additional hypoxic stress under hyperglycemic conditions that results in vascular damage leading to dysfunction or degeneration of certain neuronal cells and thus retinal ganglion cells. But no study has compared CG loss in diabetic and non-diabetic glaucoma patients.

5. Conclusion

Although studies have shown that diabetes may increase the risk of glaucoma, this has been inconsistently demonstrated. Diabetes may contribute indirectly to glaucomatous optic neuropathy (either by increasing intraocular pressure or vasculopathy) or through direct damage to the optic nerve. However, some elements of diabetes may slow the progression of glaucoma. While the relationship between diabetes and glaucoma remains controversial, prospective studies may be needed to establish a risk-cause relationship.

Thus, vigilance in the follow-up of POAG is necessary, hence the interest of new imaging techniques that are increasingly precise and will allow for an analysis of the anatomical progression but also a study of the function by the visual field and the electroretinogram.

A larger longitudinal study with a larger sample size is needed to accurately quantify the impact of diabetes on glaucomatous progression.

Conflict of Interest

The authors declare that they have no competing interests.

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