Vitreomacular Interface Abnormalities and Glaucoma in an Elderly Population (The MONTRACHET Study)

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Submitted: December 29, 2018
Accepted: April 9, 2019

Purpose. To investigate the prevalence of vitreomacular interface abnormalities (VMIAs) in a French elderly glaucomatous population.

Methods. Using a population-based study, the MONTRACHET (Maculopathy Optic Nerve nutrition neurovascular and Heart diseases) study conducted in Dijon from 2009 to 2013 in individuals older than 75 years, the prevalence of VMIAs was estimated on glaucoma patients.

Results. A total of 1130 participants (2225 eyes) were included in the study. The mean age of participants was 82.3 ± 3.8 years, and 62.74% were women. Regarding the frequency of all VMIAs, there was no statistical difference between glaucoma patients and nonglaucoma participants (51.85% vs. 53.92%, respectively, P = 0.372). In univariate analysis, vitreomacular adherences were more frequent in nonglaucoma participants (18.39% vs. 10.78%, P = 0.036). Epiretinal membranes were more frequent in the glaucomatous population (47.06% vs. 38.13%, P = 0.018). The prevalence of macular cysts was comparable in the two groups (7.84% vs. 5.64%, P = 0.262). Macular cysts were more frequent in eyes treated with preservative-free, IOP-lowering eye drops when compared with the eyes of nonglaucomatous participants treated with IOP-lowering eye drops containing a preservative (26.67% vs. 3.37% and 5.76%, respectively, P < 0.001). In multivariate analysis, these results were no longer significant.

Conclusions. The prevalence of VMIAs was high in this elderly population and similar in both glaucomatous and nonglaucomatous participants. The information provided by macular optical coherence tomography scans should be considered with caution when used for glaucoma management in elderly patients.

Keywords: glaucoma, population-based study, spectral-domain optical coherence tomography, vitreomacular interface

The emergence of optical coherence tomography (OCT) more than 2 decades ago has led to a dramatic improvement in visualizing and evaluating the vitreomacular interface and in diagnosing vitreomacular interface abnormalities (VMIAs).1 Although OCT has been shown to lead to vitreomacular adhesion or vitreomacular traction,2 Associations have also been described between PVD and epiretinal membranes.2,3 Posterior vitreous detachment is an age-related physiological event, with a high prevalence rate (around 80%) in the elderly population.4 Some reports suggest that intravitreal oxidative stress could disrupt hyaluronic acid levels, leading to vitreous liquefaction and ultimately PVD or in some cases VMIAs.5 In addition, the proliferation of glial cells, fibrous astrocytes, fibrocytes, and myofibroblasts contributes to the development of epiretinal membranes.6 Glaucoma is a chronic ocular disorder characterized by the progressive loss of retinal ganglion cells. It is the leading cause of irreversible blindness, and some estimates predict that it will affect about 112 million people worldwide by 2040.8 Several risk factors associated with glaucoma have been identified, such as family history, age, myopia, ethnicity, and elevated intraocular pressure (IOP), whereas others are still debated or remain unknown.9 Low-grade inflammation seems to play a crucial role in the pathogenesis of glaucoma, and in glaucomatous eyes, oxidative stress leads to an inflammatory response including microglial and complement activation as well as chemokine/cytokine production.10–12 For the diagnosis and follow-up of glaucoma, functional and structural tests are recommended.13 Optical coherence tomography for retinal nerve fiber layer (RNFL) measurements is the widely used test for documenting the structure of the optic nerve head. However, recent studies have indicated that additional information can be gleaned from examining changes of the macular OCT scan, with the so-called ganglion cell complex (GCC).14,15 Some authors reported that GCC thickness seems to be more sensitive than the RNFL OCT scan to detect early glaucomatous damage16,17 or for monitoring eyes with advanced glaucoma.18 Conversely, some authors did not find any difference between
the yield of RNFL and GCC capability to differentiate normal and glaucomatous eyes. Nevertheless, VMIAs are a confounding factor for the conclusions that may be drawn from GCC.

Therefore, we prompted this study to evaluate the prevalence and potential associations of VMIAs with glaucoma in an elderly population.

**MATERIALS AND METHODS**

**MONTRACHET Population**

The MONTRACHET (Maculopathy Optic Nerve and nuTrition neuroVAsCular and HEarT disease) Study was a prospective population-based study investigating the prevalence of age-related eye diseases and their relation with nutritional, environmental, and vascular factors. Participants were recruited from an ongoing population-based study, the Three-City Study, which began in 1999 and was designed to examine the relationship between vascular diseases and dementia in 9294 community-dwelling persons aged older than 65 years. The participants were selected from the electoral rolls and were urban. They lived in one of the following three French cities: Bordeaux, Dijon, or Montpellier. The MONTRACHET Study was an ancillary study conducted in Dijon and designed to estimate the frequency of eye diseases and the potential associations in individuals older than 75 years of age. The methodology of the MONTRACHET Study and the participant and nonparticipant characteristics have already been described. From October 2009 to March 2013, 1153 volunteers were included. The study was approved by the regional ethics committee and was registered as 2009-A00448-49. All participants gave their informed consent, and the study followed the tenets of the Declaration of Helsinki.

**Eye Examination**

Data were collected on lifestyle, environment, and medical history, including ophthalmic diseases and treatments. All participants underwent a complete eye examination in the Department of Ophthalmology at the Dijon University Hospital (France). The eye examination included IOP measurement with a noncontact tonometer (Tonoref II, Nidek, Gamagori, Japan), slit-lamp biomicroscopy, macular and optic disc photographs with a nonmydriatic camera (TRC-NW6S; Topcon, Tokyo, Japan), axial length measurement, central corneal thickness, and visual field measurement in screening (Frequen-Doubling Technology, Carl Zeiss Meditec, Dublin, CA, USA). Spectral-domain OCT (SD-OCT; software version 5.4.7.0; Spectralis, Heidelberg Engineering Co., Heidelberg, Germany) was performed for both the macula and the optic nerve head after pupil dilation. The high-speed resolution mode and the eye-tracking system were activated to acquire the images. For the macula, an OCT image was obtained with a 20°×15° pattern size, 19 B-scans spaced 255 μm apart, and the automatic real-time mode on. For the optic disc, the RNFL thickness acquisition was obtained with a circle diameter of 3.5 mm and 16 images with the automatic real-time function. The system automatically calculated the RNFL thickness globally and according to six segments (the superotemporal, temporal, inferotemporal, inferonasal, nasal, and superonasal segments).

**Main Outcome Parameters**

The presence of VMIAs was determined using SD-OCT and based on the macular cube. Vitreomacular adherences, vitreomacular traction, and macular holes were analyzed and classified according to the International Vitreomacular Group classification (Fig. 1). Epiretinal membranes and macular cysts were also studied (Fig. 1). Vitreomacular adherence was defined as evidence of perilfoveal vitreous cortex detachment from the retinal surface, macular attachment of the vitreous cortex within a 3-mm radius of the fovea, and no detectable change in foveal contour or underlying retinal tissues. Vitreomacular traction was defined as evidence of perilfoveal vitreous cortex detachment from the retinal surface, macular attachment of the vitreous cortex within a 3-mm radius of the fovea, and attachment associated with distortion of the foveal surface, intraretinal structural changes, and/or elevation of the fovea above the retinal pigment epithelium, but no full-thickness interruption of all retinal layers. A lamellar macular hole was defined as irregular foveal contour; defect in the inner fovea; intraretinal splitting (schisis), typically between the outer plexiform and outer nuclear layers, and preservation of an intact photoreceptor layer. A full-thickness macular hole was defined as a full-thickness foveal lesion that interrupts all macular layers from the internal limiting membrane to the
retinal pigment epithelium. A macular pseudohole was defined as invaginated or heaped foveal edges, concomitant epiretinal membrane with central opening and steep macular contour to the central fovea with near-normal central foveal thickness, and no loss of retinal tissue. As there is no international consensus, epiretinal membranes were defined as hyper-reflectivity along the surface of the internal limiting membrane. Macular cysts were defined as hyporeflective spaces with well-defined margins within the retina. A cyst was considered definitely present if it was visible in at least two consecutive B-scans and was larger than 15 μm in vertical diameter.

**Definition of Glaucoma**

Eyes were diagnosed with glaucoma as defined by the International Society for Geographical and Epidemiological Ophthalmology. Identified glaucoma eyes were reexamined with gonioscopy and a Humphrey Swedish Interactive Thresholding Algorithm 24-2 visual field (Carl Zeiss Meditec, Dublin, CA, USA). Disc photographs were interpreted in duplicate by two ophthalmologists. In case of discrepancy, the adjudication was made by a glaucoma specialist. For determining the three levels of evidence described by Foster et al., we used the 97.5th and 99.5th percentiles for the vertical cup-to-disk-ratio found in our population-based study. The 97.5 and 99.5 percentiles for the vertical cup-to-disk-ratio and vertical cup-to-disk-ratio asymmetry were 0.7, 0.2 and 0.8, 0.3, respectively.

**Statistical Analysis**

Categorical variables were expressed as n (%), and continuous variables using mean ± SD because the distribution of continuous variables was normal according to the Shapiro test. For the comparison between nonglaucoma and glaucoma participants, we used generalized estimating equation regression models to take into account intradividual correlations between the two eyes. Only associations of vitreomacular adherences, epiretinal membranes, and macular cysts with age, sex, smoking, alcohol, diabetes, ocular hypertension, cataract extraction, and axial length were estimated because they were the most prevalent.

Model A consisted of patients diagnosed with glaucoma according to the International Society for Geographical and Epidemiological Ophthalmology criteria. Model B consisted of patients who declared taking IOP-lowering eye drops. Multivariate analysis was estimated after adjustment for age, sex, cataract extraction, and axial length (with a P value < 0.10). Associations were presented as odds ratio (OR) and confidence interval (95% CI). For all tests, P values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Inc., Cary, NC, USA).

**RESULTS**

Overall, 1130 (2225 eyes) of the 1153 participants of the MONTRACHET Study with at least one available and interpretable OCT scan were included in the study (Fig. 2). The baseline demographics and clinical characteristics of participants and nonparticipants are shown in Supplementary Table 1. Nonparticipants were more likely to have a longer axial length than participants (P < 0.001). The classification of glaucoma cases was as follows: 89 primary open-angle glaucomas, 2 primary angle closure glaucomas, and 11 secondary glaucomas. For primary open-angle glaucomas, the level of evidence according to Foster was n = 56 for category 1 diagnosis, n = 32 for category 2 diagnosis, and n = 1 for category 3 diagnosis. The frequency of VMIAs in the entire population was 52.04%. Of these, the most frequent VMIAs were epiretinal membranes (38.94%), vitreomacular adherences (17.70%), and macular cysts (5.84%). In multivariate analysis taking age, sex, smoking, alcohol, diabetes, ocular hypertension, cataract extraction, and axial length into account, an increased likelihood of both vitreomacular adherences and epiretinal membranes was significantly associated with male gender, cataract extraction, and axial length (P < 0.01 for each factor, respectively). Vitreomacular adherences were significantly associated with younger age (P < 0.01), whereas epiretinal membranes were associated with older age (P < 0.01). Lastly, macular cysts were also significantly associated with older age (P = 0.04), male gender (P = 0.01), cataract extraction (P < 0.01), and axial length (P = 0.04).

**Model A**

Among the 1130 participants, 102 patients (176 eyes) were diagnosed with glaucoma and included in Model A. The baseline demographics and clinical characteristics of these participants are shown in Table 1. In univariate analysis, regarding the frequency of all VMIAs, there was no statistical difference between the glaucoma group and controls (51.85% vs. 53.92%, respectively, P = 0.372). However, the frequency of epiretinal membranes was statistically higher in the glaucoma group (47.06% vs. 38.13%, P = 0.018), whereas vitreomacular adherences were significantly less frequent (10.78% vs. 18.39%, P = 0.036; Table 2). In multivariate analysis adjusted on age, sex, cataract extraction, and axial length, those correlations were no longer significant (Table 3).

**Model B**

Among the 1130 participants, 106 patients (212 eyes) treated with IOP-lowering eye drops were included in Model B. Treatments and therapeutic classes are detailed in Supplementary Table 2. In univariate analysis, the frequency of epiretinal membranes was similar in both groups receiving IOP-lowering eye drops when compared with control (OR [95% CI] = 1.47 [0.58–3.75], P =


### Table 1. Baseline Characteristics of Participants, the MONTRACHET Study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total, N = 1130</th>
<th>Glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No, n = 1028</td>
<td>Yes, n = 102</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>390 (34.51)</td>
<td>366 (35.60)</td>
</tr>
<tr>
<td>80–85</td>
<td>477 (42.21)</td>
<td>438 (42.61)</td>
</tr>
<tr>
<td>&gt;85</td>
<td>263 (23.27)</td>
<td>224 (21.79)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>421 (37.26)</td>
<td>375 (36.48)</td>
</tr>
<tr>
<td>Smoking status, yes</td>
<td>383 (34.47)</td>
<td>343 (33.89)</td>
</tr>
<tr>
<td>Alcohol consumption, yes</td>
<td>63 (6.30)</td>
<td>57 (6.27)</td>
</tr>
<tr>
<td>Diabetes, yes</td>
<td>92 (9.21)</td>
<td>81 (8.92)</td>
</tr>
<tr>
<td>IOP &gt; 21 mm Hg</td>
<td>80 (7.08)</td>
<td>70 (6.81)</td>
</tr>
<tr>
<td>Cataract extraction, yes</td>
<td>553 (49.07)</td>
<td>485 (47.32)</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>23.42 ± 1.30</td>
<td>23.37 ± 1.27</td>
</tr>
</tbody>
</table>

* Missing data for smoking (n = 19), alcohol (n = 130), diabetes (n = 131), cataract extraction (n = 5), and axial length (n = 194). Results are displayed as number (percentages) for categorical variables and mean ± standard deviation for continuous variables.

#### DISCUSSION

This study was designed with the major objective of evaluating the association between glaucoma and VMIAs. To our knowledge, the association between VMIAs and glaucoma has not yet been reported in the literature. Although we found no differences in terms of prevalence for glaucoma and nonglaucoma eyes in VMIAs as a whole, our results contribute relevant information regarding each of the three major VMIAs (vitreomacular adhesions, epiretinal membranes, macular cysts) independently.

In univariate analysis, we found a lower prevalence of vitreomacular adhesions in the glaucoma group (10.78% when compared with controls (18.39%; P = 0.036). However, in multivariate analysis the results were no longer significant (OR [95% CI] = 0.81 [0.41–1.59], P = 0.536). In the Beijing Eye Study, incomplete PVD was defined as a persistent perifoveolar attachment, close to our definition of vitreomacular adherences. The findings reported here were congruent with this study as the authors found an association between incomplete PVD and younger age, male gender, and hyperopic refractive error. Several studies investigated the prevalence and risk factors of PVD in a healthy population. One of them reported a prevalence of 18.5% of foveal adhesion, which is comparable with our data for nonglaucomatous eyes. Schwab et al. evaluated the prevalence of PVD in glaucoma patients. The authors observed that VFD was more prevalent in patients with glaucoma compared with nonglaucomatous patients. One possible explanation is that the increased oxidative stress in patients with glaucoma may lead to vitreous changes taking into consideration the proximity between the retinal ganglion cells and the vitreous. The higher prevalence found in our study is closer to the Beaver Dam Study, which used SD-OCT as well. A recent retrospective case-series study reported an association between glaucoma and vitreomacular adhesions. However, as for vitreomacular adhesions, this was no longer significant in multivariate analysis (OR [95% CI] = 1.40 [0.91–2.15], P = 0.120). Several population-based studies have documented the prevalence of epiretinal membranes with rates ranging from 2.2% to 34.1%. The disparity between studies stems from the several methods of epiretinal membrane assessment used, including some studies that used only fundus photographs. The higher prevalence found in our study is closer to the Beaver Dam Study, which used SD-OCT as well. A recent retrospective case-series study reported an association between vitreomacular adhesions and glaucoma.
with epiretinal membranes and the severity of glaucoma.\textsuperscript{34} We are not aware of any previous studies investigating the frequency of epiretinal membranes in a glaucoma population in the frame of a population-based study. However, a very recent case-control study reported a higher prevalence of epiretinal membranes in early glaucoma.\textsuperscript{35} We hypothesized that the overactivation of glial cells in glaucomatous eyes could lead to the formation of epiretinal membranes. Indeed, activated glial cells have been well documented in experimental glaucoma models.\textsuperscript{36–38} Recently, microglial and Müller cells were identified in an in vitro culture of human epiretinal membranes, supporting the involvement of glial cells in both diseases.\textsuperscript{39}

For macular cysts, the prevalence was similar between the glaucoma group and controls. Indeed, even if microcystic macular changes in the inner nuclear layer of glaucomatous eyes have been described in the literature, this is not pathognomonic for glaucoma.\textsuperscript{40} We also found a higher prevalence of macular cysts in eyes treated with preservative-free, IOP-lowering eye drops (26.67%) versus 3.37% and 5.84% in eyes treated with IOP-lowering eye drops containing preservatives and in the entire population, respectively. One explanation could be the lower frequency of individuals receiving carbonic anhydrase inhibitors in the group treated with preservative-free, IOP-lowering eye drops (15.33%) when compared with the group treated with preservative IOP-lowering eye drops (22.47%). Indeed, it has been demonstrated that carbonic anhydrase inhibitors were useful for the treatment of macular edema, especially when taken orally.\textsuperscript{41–45} Recently, topical treatment also showed efficacy for macular edema in patients diagnosed with retinitis pigmentosa.\textsuperscript{44,45} Nevertheless, although this may explain the difference between the two groups, it still does not elucidate the high rate of macular cysts in the preservative-free, IOP-lowering eye drops group. Also, most of these preservative eye drops contain benzalkonium chloride, which is known to damage the tear film and corneal surface by inducing oxidative stress and inflammation\textsuperscript{46–50} or even impact tissues inside the eye. Yet, we were not able to confirm the potential involvement of benzalkonium chloride in the development of VMIA. Indeed, our results should be interpreted with caution considering the uneven number of eyes in the two groups and particularly the small number of eyes treated with preservative-free, IOP-lowering eye drops.

In our old cohort, a macular OCT scan revealed a VMIA in more than half of the glaucomatous population. These findings challenge the current reports on the systematic use of GCC thickness analysis on the macular OCT scan for diagnosing or monitoring glaucomatous damage.\textsuperscript{21} Indeed, previous studies have already described GCC changes in several retinal diseases, such as diabetic retinopathy\textsuperscript{51} and AMD.\textsuperscript{52,53} The GCC was analyzed using automatic segmentation without checking the accuracy of delineation of segmented retinal layers, explaining the high error rate. Recently, Muftuoglu et al.\textsuperscript{54} also reported GCC changes in patients with severe dry AMD even using the manual correction of segmentation.

One of the strengths of this study was its prospective design on a large elderly population. It also uses well-accepted definitions of both glaucoma and VMIA.\textsuperscript{1,24} The first limitation is that we included an uneven number of participants in the two groups because there were not many patients diagnosed with glaucoma or treated with IOP-lowering eye drops. Second, some data regarding lifestyle, environment, and medical history were based only on self-declaration, which may lead to information bias. Third, this study only examined a white, urban European population; therefore, the results may lead to information bias. Fourth, we could not analyze the GCC on the macular OCT scans of our cohort because automatic software for that purpose was not available at this time on the Spectralis SD-OCT.

In conclusion, the frequency of VMIA was high in this elderly population in both glaucoma and nonglaucoma eyes. Therefore, macular OCT is a fundamental tool for the follow-up of glaucomatous patients not only for GCC thickness evaluation but also for the early detection of VMIA. In addition, we could not identify any statistically significant association between glaucoma and VMIA when using multivariate analysis. Considering the high prevalence rate of VMIA in an
elderly population, this study warns macular OCT users that GCC should be interpreted with caution in elderly glaucoma-tous patients.

Acknowledgments

Supported by an interregional grant titled “Programme Hospitalier de Recherche Clinique” and the regional Council of Burgundy. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the regional ethics committee (2009-A00448-49) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure: J. Blanc, None; A. Seydou, None; I. Ben Ghezala, None; C. Deschasse, None; C. Meillon, None; A.M. Bron, Allergan (C), Baush and Lomb (C), Santen Pharmaceutical (C), Théa (C); G. Binquet, None; C. Creuzot-Garcher, Allergan (C), Baush and Lomb (C), Novartis (C), Théa (C)

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