Intraocular Pressure and Glaucomatous Optic Neuropathy in High Myopia


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PURPOSE. To examine the association between intraocular pressure (IOP) and the prevalence of glaucomatous optic neuropathy (GON) in high myopia.

METHODS. The hospital-based observational study consisted of patients treated in the Tokyo High Myopia Clinics and for whom fundus photographs and IOP readings were available. The appearance of the optic nerve head on fundus photographs was the basis for the definition of GON.

RESULTS. Among 517 eyes of 261 patients (mean age: 62.1 ± 14.2 years; range: 13–89 years; mean axial length: 29.5 ± 2.2 mm; range: 23.2–35.3 mm), GON was present in 141 eyes (27.3%; 95% confidence intervals [CIs]: 23.4, 31.0). Mean IOP did not differ significantly (P = 0.53) between the glaucoma group (14.5 ± 3.3 mm Hg; median: 14 mm Hg; range: 8–58 mm Hg) and the nonglaucomatous group (14.7 ± 2.5 mm Hg; median: 14 mm Hg; range: 6–23 mm Hg). In eyes with an axial length of ≤27.4 mm, higher presence of GON was correlated only with higher IOP (P = 0.037; odds ratio [OR]: 1.35; 95% CI: 1.02, 1.80). In eyes with an axial length of ≥27.5 mm, presence of GON was correlated with older age (P < 0.001; OR: 1.05; 95% CI: 1.03, 1.08), longer axial length (P < 0.001; OR: 1.60; 95% CI: 1.34, 1.91), shorter vertical diameter of the temporal arterial arcade (P = 0.009; OR: 0.82; 95% CI: 0.71, 0.95), and longer minimal optic disc diameter (P = 0.002; OR: 3.07; 95% CI: 1.52, 6.21). If IOP was added to the model, it was not significantly associated with the prevalence of GON (P = 0.97; OR: 1.00; 95% CI: 0.91, 1.10).

CONCLUSIONS. GON was associated with elevated IOP in myopic eyes with an axial length of ≤27.4 mm, while in more highly myopic eyes (axial length ≥27.5 mm), larger optic disc, longer axial elongation and older age—but not IOP mostly within its normal range—were factors associated with GON. Future studies may examine an abnormally low IOP to be associated with a lower GON prevalence in highly myopic eyes.

Keywords: glaucoma, intraocular pressure, high myopia, myopic maculopathy, parapapillary gamma zone, parapapillary delta zone.

The landmark study by Garway-Heath and colleagues on the effect of lowering of intraocular pressure (IOP) to preserve the visual field in patients with open-angle glaucoma, the Early Manifest Glaucoma Trial by Heijl and colleagues, and other studies have convincingly shown the association between IOP and glaucomatous optic neuropathy (GON). The association between IOP and GON has been demonstrated for glaucoma patients with elevated IOP as well as for patients with so-called “normal-pressure glaucoma” as reported by the Collaborative Normal-Tension Glaucoma Study and other investigations. However, it has remained elusive whether the association between IOP and GON is valid also in eyes with high axial myopia. Previous studies have reported that the prevalence of GON was significantly higher in myopic eyes, in particular highly myopic eyes, than in nonmyopic eyes after adjusting for parameters such as age, sex, blood pressure, and IOP. These studies did not conclude whether, and to what extent, IOP was associated with GON in these myopic eyes. That information, however, is clinically essential for the indication of an IOP-lowering therapy in highly myopic patients with glaucoma. Therefore, we conducted this study to examine in a relatively large group of myopic and highly myopic patients the association between the GON and IOP.

METHODS.
The study was conducted in the High Myopia Clinic of the Tokyo Medical and Dental University and included patients who were examined in 2012. The study, which was approved by the Ethics Committee of the Tokyo Medical and Dental University, was a retrospective observational hospital-based investigation. Availability of IOP measurements and fundus photographs of sufficient quality to allow the assessment of the optic disc and macula were the only inclusion criteria.

The patients underwent a series of ophthalmologic examinations including refractionometry, slit-lamp–based anterior segment biomicroscopy, Goldmann applanation tonometry, measurement of axial length (AL), and color fundus photography. The use of antiglaucomatous eye drops was recorded. Optic disc photographs taken under standardized stereoscopic conditions were available for some eyes, while for most eyes at least two photographs were taken and evaluated. Looking at...
both photographs of the optic disc (taken either under standardized stereoscopic conditions or under nonstandardized conditions), the three-dimensional contour of the optic cup in delineation of the neuroretinal rim and the disc border was assessed. Using the fundus photographs, we determined:

1. horizontal, vertical, minimal, and maximal diameter of the optic disc;
2. horizontal and maximal vertical diameter of parapapillary beta zone, gamma zone, and delta zone;
3. distance between the two crossing points of a line drawn vertically through the fovea and the temporal superior arterial arcade and the temporal inferior arterial arcade;
4. angle between the temporal vascular arcade and the optic disc (so-called "angle kappa");
5. number, location, maximal horizontal, and maximal vertical diameter of chorioretinal atrophic lesions;
6. distance between the fovea and the outer border of gamma zone (i.e., the border of gamma zone in direction to the fovea); and
7. disc-fovea distance, and the disc-fovea angle.

The study design has been described in detail recently. All length measurements were corrected for their dependence on the magnification of fundus images using the method of Littmann and Bennett.

Parapapillary beta zone was characterized by a location peripheral to parapapillary gamma zone and demonstrated a whitish underground with large and medium-sized choroidal vessels. Parapapillary gamma parapapillary delta were defined as whitish areas at the temporal optic disc border without underlying choriocapillaris, without middle-sized choroidal vessels and without signs of retinal pigment epithelium (Figs. 1–4). The delta zone, if detected, was located at the optic disc border (marked by the peripapillary ring), followed by gamma zone in direction to the fovea. The border between the gamma zone and delta zone was a demarcation line that ran more or less parallel to the optic disc border, in some eyes in the vicinity of the peripapillary arterial circle of Zinn-Haller.

Based on the appearance of the optic nerve head on the fundus photographs, GON was defined mainly by an abnormal shape of the neuroretinal rim. It included pronounced neuroretinal rim notches in the inferior or superior disc region, a segmental complete or almost complete, loss of neuroretinal rim in the inferior or superior disc region, or in a more advanced stage of GON, an extension of the optic cup to the optic disc border (corresponding to an almost loss of neuroretinal rim) in a large sector or the whole region of the optic nerve head (Figs. 1–4). The visibility of the retinal nerve fiber, the diameter of the retinal arteries, parapapillary alpha zone and beta zones, and IOP were not taken into account. Kinetic Goldmann visual field examinations, the results of which were available at the time of the study, were used to justify the diagnosis of GON in a subset of eyes. Criteria for these perimetric examinations to be used for the present study were use of the isopters III/4, I/4, I/3, I/2, and I/1, and plotting of the blind spot with different isopters, and performance by an experienced perimetrists.

For the definition of high myopia, two cutoff values of 26.5 mm and 27.5 mm of axial length were used. The basis for using...
the cutoff value of 26.5 mm was that in previous population- and hospital-based study investigations, eyes with an axial length of more than 26.5 mm showed a significantly enlarged optic disc, parapapillary gamma zone and delta zone, and an increased prevalence of myopic maculopathy and glaucomatous optic neuropathy. The reason to take an additional cutoff value of 27.5 mm for the differentiation between a ‘‘non-highly myopic’’ subgroup and a highly myopic subgroup was that due to the nonpopulation-based recruitment of study participants in our investigation, the group of eyes (n = 41) with an axial length of <26.5 mm was relatively small for a meaningful statistical analysis.

For statistically analyzing the measurements, we used a software program (SPSS 22.0; IBM-SPSS, Inc., Chicago, IL, USA). We first calculated the prevalence of GON in the study population. We then assessed the mean values and standard deviations of the measured parameters, stratifying the study population into the glaucomatous subgroup and the nonglaucomatous subgroup. We determined the statistical significance of differences between both subgroups applying the Student’s t-test for unpaired samples. We finally carried out a binary regression analysis, with the presence of GON as the dependent variable and as independent variables all those parameters which differed significantly different between the glaucomatous subgroup and the nonglaucomatous subgroup. We then dropped stepwise those parameters that either showed a high collinearity or which were no longer significantly associated with the presence of GON. We calculated the odds ratios (OR) and their 95% confidence intervals (CIs). All P values were two-sided and considered to be statistically significant if their value was lower than 0.05.

RESULTS

The study included 517 eyes (261 individuals) with a mean age of 62.1 ± 14.2 years (range: 13–89 years) and a mean axial length of 29.5 ± 2.2 mm (range: 23.2–35.3 mm). GON was present in 141 eyes (27.3%; 95% CI: 23.4, 31.0). Mean IOP readings (14.7 ± 2.7 mm Hg) did not differ significantly (P = 0.53) between the glaucomatous subgroup (14.5 ± 3.3 mm Hg; median: 14 mm Hg; range: 8–38 mm Hg) and the nonglaucomatous subgroup (14.7 ± 2.5 mm Hg; median: 14 mm Hg; range: 6–23 mm Hg; Fig. 5). Antiglaucomatous eye drops were taken for 208 eyes (40.2%; Tables 1, 2). There were 107 eyes that received antiglaucomatous eye drops although their optic discs were normal. They were included into the nonglaucomatous group. IOP was significantly lower in the treated group than in the untreated group (14.3 ± 3.0 mm Hg versus 14.9 ± 2.5 mm Hg; P = 0.01).

In the eyes with an axial length of ≤27.4 mm, GON was detected in 10 (12%) out of 84 eyes (Table 1). The glaucomatous subgroup as compared to the nonglaucomatous subgroup showed a higher IOP (P = 0.03) and a shorter disc-fovea distance (P = 0.045), while both subgroups did not differ (P > 0.10) in any other parameter tested (Table 1). The binary multivariate regression analysis included the presence of GON as a dependent variable and IOP and disc-fovea distance as independent variables. Due to missing statistical significance,
we dropped the disc-fovea distance ($P = 0.09$), so that eventually the presence of GON was associated only with higher IOP ($P = 0.04$; OR: 1.35; 95% CI: 1.02, 1.80). If the use of IOP-lowering eye drops was added to the list of independent parameters, the association between presence of glaucoma and higher IOP remained to be statistically significant ($P = 0.04$).

In the eyes with an axial length of $>27.4$ mm, GON was detected in 131 (30.3%) out of 302 eyes (Table 2). The glaucomatous subgroup compared to the nonglaucomatous subgroup had an older age ($P < 0.001$); a longer vertical diameter of the temporal arterial arcade ($P = 0.03$); a larger parapapillary beta zone area ($P < 0.001$); larger horizontal and vertical diameters of the gamma zone ($P < 0.001$); larger horizontal ($P = 0.009$) and vertical ($P = 0.004$) diameters of the delta zone; a longer disc-fovea distance ($P = 0.001$), a higher degree of fundus tessellation ($P < 0.001$); a higher count of chorioretinal lesions ($P = 0.04$); longer horizontal, vertical, minimal, and maximal diameters of the optic disc ($P < 0.001$); higher maximal optic disc diameter/minimal optic disc diameter ratios ($P = 0.06$); a larger angle between the maximal optic disc diameter and the horizontal ($P = 0.04$); and a higher prevalence of the use of IOP-lowering eye drops (Table 2).

In the binary multivariate regression analysis with presence of GON as a dependent variable, we dropped—due to missing statistical significance—the maximal-to-minimal optic disc diameter ratio ($P = 0.85$); horizontal disc diameter ($P = 0.98$); vertical gamma zone diameter ($P = 0.68$); horizontal delta zone width ($P = 0.61$); count of chorioretinal lesions ($P = 0.58$); degree of fundus tessellation ($P = 0.57$); beta zone area ($P = 0.44$); horizontal gamma width ($P = 0.96$); vertical delta zone width ($P = 0.71$); vertical disc diameter ($P = 0.65$); maximal disc diameter ($P = 0.55$); disc-fovea distance ($P = 0.65$); and the angle between maximal and the horizontal disc diameters ($P = 0.15$). In the final model, higher prevalence of GON was correlated with older age ($P < 0.001$); longer axial length ($P < 0.001$); shorter vertical diameter of the temporal arterial arcade ($P = 0.009$); and longer minimal optic disc diameter ($P = 0.002$; Table 3). If IOP was added to the model, it was not significantly associated with the prevalence of GON ($P = 0.97$; OR: 1.00; 95% CI: 0.91, 1.10). If IOP and use of IOP-lowering eye drops were added, higher prevalence of GON was associated with a higher prevalence of antiglaucomatous therapy ($P = 0.01$; OR: 2.00; 95% CI: 1.18, 3.40), while IOP was not significantly correlated ($P = 0.85$; OR: 1.01; 95% CI: 0.92, 1.11). If eyes with IOP-lowering therapy were excluded from the analysis, presence of glaucoma was associated with older age ($P < 0.001$; OR: 1.07; 95% CI: 1.03, 1.11) and longer axial length ($P < 0.001$; OR: 1.70; 95% CI: 1.27, 2.29), while the associations with the vertical diameter of the temporal arterial arcade ($P = 0.86$) and minimal optic disc diameter ($P = 0.21$) were no longer significant. Nor was the presence of glaucoma correlated with IOP ($P = 0.45$; OR: 0.93; 95% CI: 0.78, 1.11) in that model. Similar results were obtained if the highly myopic group was defined by an axial length of $\geq 26.5$ mm. Correspondingly, if eyes under IOP-lowering therapy were excluded, IOP in the glaucoma group (14.8 $\pm$ 2.2 mm Hg) and in the nonglaucomatous group (14.9 $\pm$ 2.5 mm Hg) did not differ significantly ($P = 0.68$).

If the number of chorioretinal lesions as surrogate for myopic maculopathy was added to the multivariate model...

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**Figure 3.** Fundus photograph of a highly myopic, glaucomatous eye with parapapillary gamma zone (white arrows) and vessel kinking (border between optic cup and neuroretinal rim) (black arrows) at the optic disc border.
(with GON as a dependent variable and with age, axial length, vertical distance of the temporal arterial, and longer minimal optic disc diameter as independent variables), it was not significantly \( (P = 0.50) \) correlated with GON.

If the multivariate analysis was repeated after the total study population was stratified into three age groups of roughly equal size (<57 years \( n = 165 \); 57–69 years \( n = 181 \); and >69 years \( n = 171 \)), similar results were obtained. For the group with an age of <57 years, higher prevalence of GON was correlated with older age \( (P = 0.04; \text{OR: } 1.10; 95\% \text{ CI: } 1.00, 1.19) \), longer axial length \( (P = 0.03; \text{OR: } 1.35; 95\% \text{ CI: } 1.03, 1.78) \) and longer minimal optic disc diameter \( (P = 0.04; \text{OR: } 3.85; 95\% \text{ CI: } 1.06, 14.0) \), but not with IOP \( (P = 0.38; \text{OR: } 0.91; 95\% \text{ CI: } 0.74, 1.12) \). For the group with an age of 57 to 69 years, higher prevalence of GON was correlated with longer axial length \( (P < 0.001; \text{OR: } 1.68; 95\% \text{ CI: } 1.32, 2.13) \), shorter vertical diameter of the temporal arterial arcade \( (P = 0.007; \text{OR: } 0.71; 95\% \text{ CI: } 0.55, 0.91) \) and longer minimal optic disc diameter \( (P = 0.04; \text{OR: } 2.89; 95\% \text{ CI: } 1.05, 7.95) \), but not with IOP \( (P = 0.32; \text{OR: } 1.07; 95\% \text{ CI: } 0.94, 1.23) \). For the group with an age of >69 years, higher prevalence of GON was correlated with longer axial length \( (P = 0.001; \text{OR: } 1.46; 95\% \text{ CI: } 1.17, 1.82) \), but not with IOP \( (P = 0.30; \text{OR: } 1.10; 95\% \text{ CI: } 0.92, 1.31) \).

In a similar manner, if all patients examined in the study were included together into the statistical analysis, higher prevalence of GON was correlated with older age \( (P < 0.001; \text{OR: } 1.04; 95\% \text{ CI: } 1.02, 1.06) \); longer axial length \( (P < 0.001; \text{OR: } 1.45; 95\% \text{ CI: } 1.26, 1.66) \); shorter diameter of the temporal arterial arcade \( (P = 0.02; \text{OR: } 0.85; 95\% \text{ CI: } 0.73, 0.98) \); longer minimal optic disc diameter \( (P = 0.002; \text{OR: } 2.84; 95\% \text{ CI: } 1.44, 5.59) \); and antiglaucomatous treatment by IOP-lowering eye drops \( (P = 0.006; \text{OR: } 2.00; 95\% \text{ CI: } 1.22, 13.28) \), while it was not significantly associated with IOP \( (P = 0.53) \). If only eyes without antiglaucomatous therapy were included, prevalence of GON was again not significantly associated with IOP \( (P = 0.97) \).

In a subset of 89 highly myopic eyes for which reliable perimetric printouts were available at the time of the study, all eyes with the diagnosis of a nonfinal stage of GON showed nasal steps inferiorly or superiorly or arcuate scotomata. All eyes showed high myopia associated perimetric defects such as central or paracentral deep or absolute scotoma or concentric visual contraction.

**DISCUSSION**

In our hospital-based study performed in a third referral myopia clinic, higher prevalence of GON was correlated with higher IOP in eyes with an axial length of \( \geq 27.4 \text{ mm} \), in contrast to highly myopic eyes (axial length \( \geq 27.5 \text{ mm} \)), in which the frequency of GON was not correlated with IOP, after adjusting for larger optic disc size, longer axial elongation, and older age.

These findings concur with results of numerous previous investigations in which the level of IOP was generally associated with GON.\(^1\)\(^-\)\(^4\)\(^,8\) The new finding of our study is that the association between the level of IOP and GON was valid mostly for myopic eyes with an axial length of \( \leq 27.4 \text{ mm} \), while in more highly myopic eyes, the association between...
FIGURE 5. Graph showing the distribution of intraocular pressure stratified by the presence of (a) glaucoma and (b) axial length.
Table 1. Morphometric Parameters of the Fundus in the Eyes With an AL ≤27.4 mm

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Glaucomatous Group</th>
<th>Nonglaucomatous Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>10</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>63.7 ± 16.8</td>
<td>64.8 ± 14.7</td>
<td>0.85</td>
</tr>
<tr>
<td>Intraocular pressure, mm Hg</td>
<td>15.9 ± 3.3</td>
<td>14.1 ± 2.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Use of IOP-lowering eye drops, yes/no</td>
<td>21/53</td>
<td>4/6</td>
<td>0.48</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>26.3 ± 0.9</td>
<td>26.2 ± 1.2</td>
<td>0.67</td>
</tr>
<tr>
<td>Vertical diameter of temporal arterial arcade, mm</td>
<td>7.71 ± 0.80</td>
<td>7.23 ± 1.48</td>
<td>0.21</td>
</tr>
<tr>
<td>Angle kappa between temporal superior arterial arcade and temporal inferior arterial arcade, degrees</td>
<td>103 ± 15</td>
<td>102 ± 17</td>
<td>0.82</td>
</tr>
<tr>
<td>Parapapillary beta zone area, mm²</td>
<td>3.25 ± 2.55</td>
<td>3.54 ± 2.94</td>
<td>0.77</td>
</tr>
<tr>
<td>Parapapillary gamma zone, horizontal diameter, mm</td>
<td>1.79 ± 1.61</td>
<td>2.12 ± 1.22</td>
<td>0.23</td>
</tr>
<tr>
<td>Parapapillary gamma zone, vertical diameter, mm</td>
<td>1.63 ± 1.47</td>
<td>2.05 ± 1.22</td>
<td>0.41</td>
</tr>
<tr>
<td>Parapapillary delta zone, horizontal diameter, mm</td>
<td>1.44 ± 1.26</td>
<td>1.90 ± 0.99</td>
<td>0.30</td>
</tr>
<tr>
<td>Parapapillary delta zone, vertical diameter, mm</td>
<td>2.18 ± 0.34</td>
<td>2.30 ± 0.55</td>
<td>0.16</td>
</tr>
<tr>
<td>Disc-fovea angle with horizontal, degrees</td>
<td>7.7 ± 5.5</td>
<td>10.2 ± 5.5</td>
<td>0.23</td>
</tr>
<tr>
<td>Angle between disc-fovea line and maximal optic disc diameter line, degrees</td>
<td>80.3 ± 41.9</td>
<td>97.2 ± 36.5</td>
<td>0.28</td>
</tr>
<tr>
<td>Disc-fovea distance, mm</td>
<td>4.71 ± 0.22</td>
<td>4.92 ± 0.57</td>
<td>0.045</td>
</tr>
<tr>
<td>Fundus tesselation</td>
<td>2.89 ± 0.60</td>
<td>2.84 ± 0.84</td>
<td>0.82</td>
</tr>
<tr>
<td>Count of chorioretinal lesions</td>
<td>0.7 ± 1.1</td>
<td>0.3 ± 0.7</td>
<td>0.27</td>
</tr>
<tr>
<td>Optic disc, horizontal diameter, mm</td>
<td>1.49 ± 0.26</td>
<td>1.37 ± 0.29</td>
<td>0.21</td>
</tr>
<tr>
<td>Optic disc, vertical diameter, mm</td>
<td>1.57 ± 0.22</td>
<td>1.54 ± 0.29</td>
<td>0.66</td>
</tr>
<tr>
<td>Optic disc, minimal diameter, mm</td>
<td>1.24 ± 0.25</td>
<td>1.22 ± 0.27</td>
<td>0.85</td>
</tr>
<tr>
<td>Optic disc, maximal diameter, mm</td>
<td>1.78 ± 0.16</td>
<td>1.79 ± 0.28</td>
<td>0.92</td>
</tr>
<tr>
<td>Optic disc, vertical diameter / horizontal diameter</td>
<td>1.11 ± 0.41</td>
<td>1.16 ± 0.28</td>
<td>0.77</td>
</tr>
<tr>
<td>Optic disc, maximal diameter / minimal diameter</td>
<td>1.52 ± 0.53</td>
<td>1.51 ± 0.36</td>
<td>0.98</td>
</tr>
<tr>
<td>Angle between maximal optic disc diameter line and horizontal line, degrees</td>
<td>72.7 ± 42.3</td>
<td>89.1 ± 37.8</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Table 2. Morphometric Parameters of the Fundus in the Eyes With an AL >27.5 mm

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Glaucomatous Group</th>
<th>Nonglaucomatous Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>131</td>
<td>302</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>66.2 ± 11.7</td>
<td>59.5 ± 14.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraocular pressure, mm Hg</td>
<td>14.4 ± 3.2</td>
<td>14.9 ± 2.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Use of IOP-lowering eye drops, yes/no</td>
<td>80/51</td>
<td>103/199</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>31.2 ± 1.9</td>
<td>29.8 ± 1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vertical diameter of temporal arterial arcade, mm</td>
<td>7.68 ± 1.86</td>
<td>8.16 ± 1.67</td>
<td>0.03</td>
</tr>
<tr>
<td>Angle kappa between temporal superior arterial arcade and temporal inferior arterial arcade, degrees</td>
<td>90 ± 21</td>
<td>90 ± 16</td>
<td>0.96</td>
</tr>
<tr>
<td>Parapapillary beta zone area, mm²</td>
<td>9.3 ± 8.1</td>
<td>6.2 ± 6.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Parapapillary gamma zone, horizontal diameter, mm</td>
<td>3.76 ± 2.54</td>
<td>3.05 ± 1.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parapapillary gamma zone, vertical diameter, mm</td>
<td>3.80 ± 2.68</td>
<td>2.80 ± 1.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parapapillary delta zone, horizontal diameter, mm</td>
<td>2.53 ± 1.57</td>
<td>2.12 ± 1.19</td>
<td>0.009</td>
</tr>
<tr>
<td>Parapapillary delta zone, vertical diameter, mm</td>
<td>2.95 ± 1.95</td>
<td>2.38 ± 1.38</td>
<td>0.004</td>
</tr>
<tr>
<td>Disc-fovea angle with horizontal, degrees</td>
<td>8.4 ± 5.3</td>
<td>9.0 ± 5.3</td>
<td>0.28</td>
</tr>
<tr>
<td>Angle between disc-fovea line and maximal optic disc diameter line, degrees</td>
<td>93 ± 86</td>
<td>89 ± 26</td>
<td>0.15</td>
</tr>
<tr>
<td>Disc-fovea distance, mm</td>
<td>5.99 ± 0.87</td>
<td>5.69 ± 0.69</td>
<td>0.001</td>
</tr>
<tr>
<td>Fundus tesselation</td>
<td>2.84 ± 0.86</td>
<td>5.22 ± 0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Count of chorioretinal lesions</td>
<td>0.9 ± 1.1</td>
<td>0.7 ± 1.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Optic disc, horizontal diameter, mm</td>
<td>1.76 ± 0.50</td>
<td>1.52 ± 0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Optic disc, vertical diameter, mm</td>
<td>2.23 ± 0.56</td>
<td>1.95 ± 0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Optic disc, minimal diameter, mm</td>
<td>1.59 ± 0.45</td>
<td>1.37 ± 0.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Optic disc, maximal diameter, mm</td>
<td>2.48 ± 0.52</td>
<td>2.21 ± 0.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Optic disc, vertical diameter/horizontal diameter</td>
<td>1.32 ± 0.35</td>
<td>1.34 ± 0.34</td>
<td>0.54</td>
</tr>
<tr>
<td>Optic disc, maximal diameter/minimal diameter</td>
<td>1.63 ± 0.38</td>
<td>1.70 ± 0.43</td>
<td>0.06</td>
</tr>
<tr>
<td>Angle between maximal optic disc diameter line and horizontal line, degrees</td>
<td>86 ± 29</td>
<td>80 ± 27</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Stratified into eyes with glaucoma and eyes without glaucoma.

GON and IOP was not quite clear, neither before nor after adjusting for using IOP-lowering eyes drops. Previous population-based studies and hospital-based studies showed that a relatively large number of patients with GON had IOP measurements within the statistically normal range so that the term of normal-pressure glaucoma was formed. However, also in these patients, despite having a normal IOP, the presence of GON was associated with a higher level of IOP.
Table 3. Associations (Multivariate Analysis) of the Prevalence of GON in Eyes With an AL > 27.5 mm

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio</th>
<th>95% CI of OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>&lt;0.001</td>
<td>1.05, 1.08</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>&lt;0.001</td>
<td>1.60, 1.91</td>
</tr>
<tr>
<td>Minimal optic disc diameter, mm</td>
<td>0.009</td>
<td>3.07, 1.52, 0.21</td>
</tr>
<tr>
<td>Vertical diameter of the temporal arterial arcade, mm</td>
<td>0.002</td>
<td>0.82, 0.71, 0.95</td>
</tr>
</tbody>
</table>

Most of these studies did not include highly myopic eyes nor specifically addressed the highly myopic group of patients within their study populations. Other investigations, including population-based studies, showed that high myopia was a risk factor for the presence of GON after adjusting for IOP and other parameters. These studies, however, did not evaluate whether the prevalence of GON was associated with the level of IOP in the highly myopic study participants.

In the present study we used two cutoff values of axial length for the definition of high myopia, a value of 26.5 mm and a value of 27.5 mm. In previous studies, the value of 26.5 mm (or a refractive error of −8 diopters) had separated eyes without marked enlargement of the optic disc from eyes with enlargement of the optic disc; eyes without enlargement of the parapapillary gamma zone and delta zone from eyes with enlargement of gamma and delta zones, eyes without myopic maculopathy from eyes with myopic maculopathy, and eyes with a normal age-adjusted prevalence of open-angle glaucoma from eyes with a markedly increased prevalence of glaucomatous optic neuropathy. Since our study did not have a population-based recruitment of study participants, the group of eyes (n = 41) with an axial length of less than 26.5 mm was relatively small for a meaningful statistical analysis. We therefore used an additional cutoff value of 27.5 mm, to have a “non-highly” myopic subgroup sufficiently large for statistical analysis. Without a doubt, this was a compromise, since this enlarged non-highly myopic subgroup will have included some eyes with high myopia. However, since the borderline between medium myopia and high myopia is not sharply delineated nor has it officially been defined, we performed a parallel analysis with this second cutoff value of 27.5 mm. Also using the cutoff value of 27.5 mm led to a markedly even distribution of the study population into a “non-highly” myopic subgroup (n = 84) and a highly myopic subgroup (n = 433; Tables 1, 2). However, it was not the purpose of the study to compare two equally sized subgroups of individuals but to compare a nonhighly myopic subgroup with a highly myopic subgroup.

If the presence of GON in the highly myopic study population of our investigation was not correlated with IOP, the question arises whether the optic nerve damage observed in the glaucomatous patients in the highly myopic group was indeed glaucomatous or whether it should be termed in a different way. From a morphologic point of view, the eyes fulfilled the main criterion for the definition of GON (i.e., an abnormally small and abnormally shaped neuroretinal rim and, as a corollary, an abnormally large optic cup with a vessel kinking at the optic disc border; Figs. 1–4). The results of the present study suggest performing a prospective randomized trial assessing the potential effect of an IOP-lowering therapy in highly myopic patients with glaucoma-like optic disc morphology.

The reasons for the lack of an elevated IOP and GON in the highly myopic eyes of our study have remained unclear so far. Previous studies have demonstrated marked anatomic particularities of the optic nerve head in highly myopic eyes, such as an axial elongation associated enlargement of the optic disc; widening of the papillary Bruch’s membrane opening and its translocation in direction to the macula, elongation, and thinning of the lamina cribrosa; a steeper translamina cribrosa pressure gradient due to the decreased lamina cribrosa thickness, a flattening of the optic disc, development, and enlargement of the parapapillary gamma zone (defined as parapapillary region free of Bruch’s membrane) and delta zone (defined as region of an elongated and thinned peripapillary scleral flange); a decreased peripapillary choroidal thickness; a longer distance between the peripapillary arterial circle Zinn-Haller and the lamina cribrosa nourished by the arterial ring, and peripapillary suprachoroidal cavitations. In particular, the thinning and stretching of the lamina cribrosa and the elongation and thinning of the peripapillary scleral flange may be of importance for an increased susceptibility of the highly myopic optic nerve head for optic nerve damage. The peripapillary scleral flange is the biomechanical anchor of the lamina cribrosa and any change in its proportions may lead to a change in its biomechanical properties. In that context, the difference in scleral compliance between highly myopic eyes and nonhighly myopic eyes may play a role for an increased susceptibility of a highly myopic optic nerve head. An additional factor may be the optic nerve dura mater strain on the optic nerve head of highly myopic eyes.

When discussing the findings obtained in our study, its limitations have also to be taken into account. First, the diagnosis of GON was based on the ophthalmoscopic appearance of the optic nerve head, without taking into account results of visual field examinations or findings obtained by optical coherence tomography. In view of a high interobserver variation in assessing the optic nerve head and in view of the ongoing discussion of a commonly accepted definition of glaucomatous optic neuropathy, the distinction between eyes with a normal optic nerve and eyes with GON in our study may be doubted. It may be taken into account, however, that perimetric results obtained in highly myopic eyes can be treacherous for the diagnosis of GON since visual field defects in highly myopic eyes can be caused by a multitude of reasons besides glaucoma, including choroidal and retinal changes due to myopic axial elongation. Due to the retrospective character of the study design, optical coherence tomographic (OCT) images of the optic nerve head were not available. However, OCT images would not have been very helpful since spectral-domain OCT images do not allow a clear distinction between a normal optic nerve and GON in the majority of highly myopic eyes. Intraocular pressure was not taken as criterion for the definition of GON, since previous investigations, including population-based studies from East Asia, had shown that a single IOP measurement was within the statistically normal range in the majority of patients with GON. Also, since IOP was one of the main outcome parameters, it could not be taken as a criterion for the definition of GON. Second, it may also be considered that for the diagnosis of GON as applied in our study, the neuroretinal rim had to have a clearly glaucoma-like appearance, either in the form of marked rim notches touching or almost touching the disc border or in the form of an advanced loss of neuroretinal rim with an optic cup extending to the disc border for a large sector of the optic nerve head (Figs. 1–4). This definition of GON might have led to an underestimation of the prevalence of GON since early stages of glaucoma, before the development of clear neuroretinal rim notches, might have been considered to be nonglaucomatous. It may have partly compensated for the weakness in the study design that visual field defects were not used for the definition of GON. Third, central corneal thickness measurements were not available so...
that the IOP readings could not be corrected for their
dependence on corneal thickness.\textsuperscript{29,30} Previous studies have shown,
however, that central corneal thickness does not depend
on axial length, so that this limitation in our study
design not having corneal thickness measurements might have
led to a higher variability in the IOP readings but may not have
markedly influenced the results and conclusions of the study.\textsuperscript{31}

Fourth, the study was carried in a nationally well-known third-
referral center for myopia, so that the study population
may not have been representative for the general myopic or highly
myopic population. The recruitment of the study participants
may therefore have caused a bias. The study participants
attended the hospital and were included into the study based
on their myopia, while glaucoma was not a reason for
attending the hospital. Fifth, the study population consisted
only of Japanese, so that potential interethnic differences have
to be taken into account when transferring the results onto
other countries or world regions. Sixth, some of the disc
photographs were taken in a nonstereoscopic manner. There
were, however, usually at least two photographs for each optic
disc available, so that the simultaneous observation of both
optic disc images allowed some stereoscopic analysis. Seventh,
if the observation of a missing association between IOP and
GON in the highly myopic group in the present study
population is valid, it will not indicate that there is no such
association. It could be that highly myopic glaucomatous eyes
as compared with nonhighly myopic glaucomatous eyes have a
markedly lower IOP threshold to develop optic nerve damage.
It could indicate that an IOP of perhaps lower than 10 mm Hg
might be necessary to prevent the development of GON in
these highly myopic eyes. Such low IOP values were not
measured in the highly myopic population of the present study
so that a potential association between very low IOP and lower
prevalence of GON in high myopia could not be assessed in
this study. One might discuss that in highly myopic eyes with
axial elongation, associated enlargement and stretching of the
optic disc and parapapillary region as the main risk factors for
GON in high myopia a normal IOP may be sufficient to lead to
GON, and that potentially a very low IOP—perhaps lower than
10 mm Hg—may be necessary for the therapy of such a
condition.\textsuperscript{31,32} Eighth, one may take into account that
individuals classified as nonglaucomatous, in particular those
with an axial length of more than 27.5 mm and who were
younger than those individuals classified as glaucomatous, may
eventually develop glaucomatous optic neuropathy later in
their life. It might have led a partial misclassification bias.
Ninth, the glaucomatous group as compared to the non-
glaucomatous group had a significantly higher prevalence of
antiglaucomatous therapy while the IOP did not differ
significantly between both groups with an axial length >27.5
mm (Table 2). It could suggest that the lack of a difference in
IOP between both groups was due to the higher prevalence of
IOP-lowering therapy in the glaucomatous group. In the
multivariate analysis with adjustment for the prevalence of
antiglaucomatous treatment, however, the IOP was not
significantly associated with the glaucomatous versus non-
glaucoma group. Tenth, IOP, in particular if measured only
once, may be only one out of several parameters influencing
the glaucoma susceptibility of the retinal ganglion cell axons
when passing through the lamina cribrosa. In particular, for
highly myopic eyes, additional parameters such as IOP
fluctuation, blood pressure, and central corneal thickness, to
determine a few, may play a role; however, they were not assessed
in the present retrospective study. Eleventh, due to its cross-
sectional character, the present study could not assess at which
time and at which axial length GON started to develop. Since
axial length, in particular in medium and highly myopic eyes,
tends to further increase over time, one cannot exclude the
possibility that GON developed at an axial length of less than
27.5 mm while when included into the present study the axial
length exceeded 27.5 mm so that the eye was included into the
highly myopic group. Future prospective studies with follow-
up examinations of the study participants may avoid these
limitations of the present investigation.

In conclusion, GON is associated with elevated IOP in
myopic eyes with an axial length of ≤27.4 mm, while in more
highly myopic eyes (axial length >27.5 mm), larger optic disc,
axial elongation, and older age, but not IOP mostly within its
normal range, were factors associated with GON. Future
studies may address whether an abnormally low IOP would be
associated with a lower prevalence of GON in highly myopic
eyes.

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