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Title
Systemic Factors Influence the Prognosis of Diabetic Macular Edema after Pars Plana Vitrectomy with Internal Limiting Membrane Peeling

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Systemic factors influence the prognosis of diabetic macular edema after pars plana vitrectomy with internal limiting membrane peeling

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Running title: Systemic factors influence DME prognosis
Acknowledgments

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Abstract

Background: To evaluate the prognostic factors for the best corrected visual acuity (BCVA) and foveal average retinal thickness after vitrectomy with internal limiting membrane (ILM) peeling for diabetic macular edema. Design: Retrospective, single-centre study. Participants: This study involved 31 eyes of 27 patients who had undergone vitrectomy with ILM peeling between January 2005 and March 2008. Methods: Relationships between preoperative systemic or ocular factors and BCVA or foveal average retinal thickness before and 6 months after the operation were evaluated. Main Outcome Measures: BCVA and foveal average retinal thickness before and 6 months after the operation. Results: Mean logMAR (logarithm of the minimum angle of resolution) improved from 0.84±0.64 (mean±standard deviation) preoperatively to 0.64±0.38 6 months postoperatively (P=0.393). Foveal average retinal thickness significantly improved from 473±146 μm preoperatively to 318±108 μm 6 months after the operation (P<0.0001). Preoperative foveal average retinal thickness was significantly thicker with cardiovascular disease or cerebral infarction (P=0.0019) or cystoid macular edema (P=0.0028), while preoperative BCVA was significantly lower when epiretinal membrane (P=0.042) was present. Foveal
average retinal thickness at the 6-month follow-up was significantly thicker when patients had a higher body mass index (P=0.0088), were not on dialysis (P=0.012), or did not have proliferative diabetic retinopathy (P=0.013). BCVA at the 6-month follow-up was significantly lower in the group with no history of diabetes treatment until diabetic retinopathy was found (P=0.023) and in patients with a higher preoperative glycosylated hemoglobin (P=0.033). **Conclusions:** Preoperatively, BCVA and foveal average retinal thickness were primarily associated with ocular factors, while they were strongly associated with systemic factors, postoperatively. Ocular factor improvements may be related to the surgical procedure.

**Key words:** diabetic macular edema, vitrectomy, glycosylated hemoglobin, foveal average retinal thickness
Introduction

Diabetic retinopathy (DR) is the leading cause of legal blindness in many countries.[1] Complications of DR such as macular edema (ME), vitreous hemorrhage, tractional retinal detachment, or neovascular glaucoma can be present. Diabetic macular edema (DME) is one of the common causes of visual loss, and it is normally treated by focal photocoagulation,[2, 3] triamcinolone acetonide,[4] and anti-vascular endothelial growth factor (VEGF).[5]


Several studies have reported that PPV was able to effectively improve ME and visual acuity in some, but not all, cases of DME.[17-25] Some of these studies have also demonstrated that systemic risk factors are important for the prognosis of DME after PPV.[18, 24] However, to the best of our knowledge,
there are no reports of any specific systemic factors that can influence the prognosis of DME after PPV with ILM peeling, which is a recently developed advanced technique. Therefore, the current study was designed to evaluate potential DME prognostic factors for the best corrected visual acuity (BCVA), and the foveal average retinal thickness after PPV with ILM peeling.

**Materials and Methods**

PPV with ILM peeling was performed in 37 eyes of 30 DME patients by four surgeons between January 2005 and March 2008 at Nagasaki University. We performed PPV with ILM peeling for cases with 0.155 or less logMAR (logarithm of the minimal angle of resolution), with continuous diffuse ME more than 6 months, and with thicker posterior hyaloids membrane suspected. All patients did not undergo panretinal photocoagulation or macular photocoagulation within 3 months before PPV with ILM peeling. After patient enrollment, we excluded 4 eyes that had no preoperative retinal thickness measurements, 1 eye with a postoperative macular hole, and 1 eye in which there were no retinal thickness measurements for 6 months postoperatively, resulting in a total of 31 eyes of 27 patients being examined in the study. None of the patients had vitreo-macular
traction syndrome or received any adjunctive treatment, such as anti-VEGF or triamcinolone acetonide. Foveal average retinal thicknesses were determined by using optical coherence tomography (OCT) (Cirrus®, Carl Zeiss Meditec, Dublin, CA) to measure the central subfield mean thickness. BCVA, fundus examinations, and foveal average retinal thickness before and 6 months after operations were reviewed retrospectively using the patients’ clinical records.

The relationships between preoperative systemic or ocular factors and BCVA or foveal average retinal thickness before and 6 months after the operation were statistically evaluated. Systemic factors examined included age, sex, BMI, systolic blood pressure, hypertension, hyperlipidemia, dialysis, cardiovascular disease, cerebral infarction, no diabetes treatment history until diabetic retinopathy was found (no diabetes treatment), and preoperative blood test results. A blood test that measured hemoglobin (Hb), hematocrit (Hct), total protein (TP), albumin (alb), creatinine, blood urea nitrogen (BUN), creatinine clearance (Ccr), and glycosylated hemoglobin (HbA1c) was performed 1 month before surgery as the standard preoperative assessment. The ocular factors examined included the type of macular edema (cystoid or not)[25, 26], proliferative diabetic retinopathy (PDR), foveal hard exudates, and the presence
of epiretinal membrane (ERM) without fibrovascular components prior to the operation. BCVA, fundus examination, and optical coherence tomography (OCT) were all performed pre- and postoperatively up until 6 months after the operation.

Statistical analysis: The results are expressed as means±standard deviation. The Mann Whitney test was used to compare the BCVA and foveal average retinal thickness before and after the operation. Multiple regression analysis was used to evaluate BCVA and foveal average retinal thickness, which were related to the above-mentioned systemic and ocular factors. Statistical analysis was performed using StatFlex ver. 5.0 software. Statistical significance was set at P<0.05.

The Ethics Committee of Nagasaki University School of Medicine approved this study.

Results

This study examined 31 eyes of 27 patients (7 females, 20 males; mean age at operation, 59±10 years). Table 1 shows the characteristics of the DME.
patients prior to the operation. While the mean logMAR improved from $0.84 \pm 0.64$ before the operation to $0.64 \pm 0.38$ at 6 months after the operation, this difference was not significant ($P=0.393$) (Figure 1). Foveal average retinal thickness significantly improved from $473 \pm 146 \, \mu m$ before the operation to $318 \pm 108 \, \mu m$ 6 months after the operation ($P<0.0001$) (Figure 2). Table 2 shows the relationship between the BCVA or foveal average retinal thickness (before and 6 months after the operation), and the preoperative systemic or ocular factors. Patients with cardiovascular disease or cerebral infarction ($P=0.0019$) or with cystoid macular edema (CME) ($P=0.0028$) had significantly thicker preoperative foveal average retinal thicknesses, while patients with ERM had a significantly lower preoperative BCVA ($P=0.042$). Additionally, patients who had a higher BMI ($P=0.0088$), were not on dialysis ($P=0.012$), or did not have proliferative diabetic retinopathy ($P=0.013$) all exhibited a significantly thicker foveal average retinal thickness at the 6-month follow-up. BCVA at the 6-month follow-up was significantly lower in both the group with no diabetes treatment history until diabetic retinopathy was found ($P=0.023$), and in the patients that had a higher HbA1c prior to the operation ($P=0.033$). There were 19 cases that used indocyanine green staining during the ILM peeling, although this was not
significantly correlated to the BCVA or retinal thickness. When the surgical
technique was examined, no statistical correlations were noted between the
surgeons and the BCVA or retinal thickness.

Discussion

This study demonstrated there was a significant improvement of the foveal
average retinal thickness after PPV with ILM peeling. However, while the BCVA
was maintained, this improvement was not statistically significant. These results
are similar to previous reports.[21, 23] The reason behind these findings may
potentially be due to prolonged DME or the irreversible loss that is caused by the
disruption of the photoreceptor inner/outer segment junction.[27] This suggests
that a better visual acuity prognosis could potentially be achieved if DME
operations were performed much earlier and at a time before the irreversible
visual loss occurs.

Preoperative retinal thickness was thicker when cardiovascular disease or
cerebral infarction was present, while poor glycemic control resulted in lower
postoperative BCVA. Additionally, postoperative retinal thickness was thicker in
patients with a higher BMI or when they were not on dialysis. It also has been
reported that DME improved in conjunction with improvement of anemia[10] and serum lipid levels,[14] or when patients started dialysis.[16] Studies have also reported that cardiovascular disease,[13] glycemic control,[6-9, 12] and higher BMI[9] were all risk factors for DR or DME. The present findings are consistent with these reports, as we found ischemic disease, poor glycemic control, higher BMI, and renal dysfunction to be risk factors for DME.

Preoperative BCVA was lower with ERM, while preoperative retinal thickness was thicker with CME, and postoperative retinal thickness was thicker without PDR. This suggests that the lower preoperative BCVA could be related to the macular dysfunction caused by ERM, while the increased preoperative retinal thickness could be due to the retinal protrusion from the cystic changes. However, macular traction due to ERM can be improved by the PPV operation, and retinal thickness would thus also be improved. On the other hand, DME that occurs without PDR preoperatively might be caused by an unknown etiology, with the mechanism of DME also differing from that seen for PDR.

In summary, ocular factors such as ERM and CME were correlated with both the preoperative BCVA and retinal thickness, while BCVA and retinal thickness were primarily correlated with systemic factors such as no diabetes
treatment, HbA1c level, BMI, and dialysis, postoperatively. These results additionally suggest that there is an improvement in the ocular factors after PPV with ILM peeling. Even though the BCVA improvement was not statistically significant in the current study, the fact that the ocular factors improved after PPV is an important discovery in and by itself. Furthermore, the present data indicate that improvement of systemic factors may be just as important as the ocular factor improvements.

Interestingly, there were no factors that were correlated with both the BCVA and the foveal average retinal thickness. However, as has been previously reported, BCVA is not always correlated with the foveal average retinal thickness. For example, a poor BCVA is seen when there are subfoveal hard exudates,[25] and foveal atrophy has been shown to be associated with a decreased retinal thickness.[28]

The limitations of the current study include the small number of patients and the lack of any evaluation of the systemic risk factors 6 months after the operation. Therefore, the possibility exists that at 6 months after the operation, there was an improvement of the postoperative foveal average retinal thickness due to glycemic control or positive changes in the blood test results. To clarify
the current results, further studies that examine larger numbers of DME cases
after PPV with ILM peeling will need to be undertaken.

In conclusion, foveal average retinal thickness significantly improved after
PPV with ILM peeling. And our results show that the BCVA and foveal average
retinal thickness were primarily associated with ocular factors preoperatively,
while postoperatively, they were strongly associated with systemic, but not
ocular factors. These changes may additionally be related to improvement of the
ocular factors that result after the operation. Since BCVA at 6 months after the
operation was significantly correlated with the preoperative blood glucose
control, control of diabetes itself may be a very important step in establishing a
better DME prognosis after PPV with ILM peeling. The limitations of the current
study include the small number of patients and the lack of any evaluation of the
systemic risk factors 6 months after the operation.

References

3 Scott IU, Danis RP, Bressler SB, Bressler NM, Browning DJ, Qin H: Effect of


Figure Legends

Figure 1. Mean logarithm of the minimum angle of resolution (LogMAR) before and 6 months after pars plana vitrectomy with internal limiting membrane peeling. While visual acuity improved from 0.84±0.64 before the operation to 0.64±0.38 at 6 months after the operation, this difference was not significant (P=0.393).

Figure 2. Mean foveal average retinal thickness before and 6 months after pars plana vitrectomy with internal limiting membrane peeling. Foveal average retinal thickness significantly improved from 473±146 μm preoperatively to 318±108 μm 6 months postoperatively (P<0.0001).

LogMAR= logarithm of the minimum angle of resolution
Figure 1.
Figure 2.
<table>
<thead>
<tr>
<th>Systemic factors</th>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>20:7</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>59±10</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.7±2.8</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137±22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
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<tr>
<td>Dialysis</td>
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<td>Cardiovascular disease</td>
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<td>Cerebral infarction</td>
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<td>No treatment for diabetes</td>
<td>17</td>
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</tbody>
</table>

**Blood test results** (mean±SD)

<table>
<thead>
<tr>
<th>Blood test result</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.7±1.7 (11.3-15.2)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>38.1±4.8 (33.4-44.9)</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>6.9±0.5 (6.7-8.3)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.1±0.4 (4.0-5.0)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>19.2±9.1 (8-22)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.25±1.56 (0.4-1.1)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>82±36 (80-110)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.0±1.59 (4.3-5.8)</td>
</tr>
</tbody>
</table>

**Ocular factors**

<table>
<thead>
<tr>
<th>Ocular factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystoid macular edema</td>
<td>11</td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy</td>
<td>7</td>
</tr>
<tr>
<td>Foveal hard exudates</td>
<td>4</td>
</tr>
<tr>
<td>Epiretinal membrane</td>
<td>5</td>
</tr>
</tbody>
</table>

SD=standard deviation
HbA1c=glycosylated hemoglobin
No diabetes treatment=No history of diabetes treatment until diabetic retinopathy was found
Blood test results ()=normal range in Japanese
TABLE 2. Relationships between best corrected visual acuity or foveal average retinal thickness and systemic or ocular factors pre- and postoperatively

<table>
<thead>
<tr>
<th>Dependent factors</th>
<th>Independent factors</th>
<th>Regression coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative</strong></td>
<td>Epiretinal membrane</td>
<td>-0.634</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>cardiovascular disease or cerebral infarction</td>
<td>196.75</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Cystoid macular edema</td>
<td>145.06</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td>No treatment for diabetes</td>
<td>-0.308</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>HbA1c before operation</td>
<td>-0.091</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>Body mass index</td>
<td>17.44</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Dialysis</td>
<td>-162.63</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>Proliferative diabetic retinopathy</td>
<td>-108.82</td>
<td>0.013</td>
</tr>
</tbody>
</table>

BCVA=best corrected visual acuity
No diabetes treatment=no history of diabetes treatment until diabetic retinopathy was found
HbA1c=glycosylated hemoglobin