

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

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18 Running title: Systemic factors influence DME prognosis

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26

27 **Abstract**

28 **Background:** To evaluate the prognostic factors for the best corrected visual
29 acuity (BCVA) and foveal average retinal thickness after vitrectomy with internal
30 limiting membrane (ILM) peeling for diabetic macular edema. **Design:**
31 Retrospective, single-centre study. **Participants:** This study involved 31 eyes of
32 27 patients who had undergone vitrectomy with ILM peeling between January
33 2005 and March 2008. **Methods:** Relationships between preoperative systemic
34 or ocular factors and BCVA or foveal average retinal thickness before and 6
35 months after the operation were evaluated. **Main Outcome Measures:** BCVA
36 and foveal average retinal thickness before and 6 months after the operation.
37 **Results:** Mean logMAR (logarithm of the minimum angle of resolution) improved
38 from 0.84 ± 0.64 (mean \pm standard deviation) preoperatively to 0.64 ± 0.38 6 months
39 postoperatively ($P=0.393$). Foveal average retinal thickness significantly
40 improved from 473 ± 146 μm preoperatively to 318 ± 108 μm 6 months after the
41 operation ($P < 0.0001$). Preoperative foveal average retinal thickness was
42 significantly thicker with cardiovascular disease or cerebral infarction ($P=0.0019$)
43 or cystoid macular edema ($P=0.0028$), while preoperative BCVA was
44 significantly lower when epiretinal membrane ($P=0.042$) was present. Foveal

45 average retinal thickness at the 6-month follow-up was significantly thicker when
46 patients had a higher body mass index ($P=0.0088$), were not on dialysis
47 ($P=0.012$), or did not have proliferative diabetic retinopathy ($P=0.013$). BCVA at
48 the 6-month follow-up was significantly lower in the group with no history of
49 diabetes treatment until diabetic retinopathy was found ($P=0.023$) and in patients
50 with a higher preoperative glycosylated hemoglobin ($P=0.033$). **Conclusions:**
51 Preoperatively, BCVA and foveal average retinal thickness were primarily
52 associated with ocular factors, while they were strongly associated with systemic
53 factors, postoperatively. Ocular factor improvements may be related to the
54 surgical procedure.

55

56 Key words: diabetic macular edema, vitrectomy, glycosylated hemoglobin, foveal
57 average retinal thickness

58

59 Introduction

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

66 Systemic risk factors for DR include glycemic control,[6-9] duration of
67 diabetes,[8, 9] body mass index (BMI),[9] higher blood pressure,[8] and
68 anemia.[10, 11] Systemic risk factors for DME include glycemic control,[12]
69 higher blood pressure,[12, 13] hyperlipidemia,[14] anemia,[15] renal disease
70 (proteinuria),[12, 16] and cardiovascular disease.[13] Ocular risk factors for DME
71 include advanced retinopathy,[13] vitreo-macular adhesion,[13] and residual
72 internal limiting membrane (ILM) after par plana vitrectomy (PPV).[17]

73 Several studies have reported that PPV was able to effectively improve ME
74 and visual acuity in some, but not all, cases of DME.[17-25] Some of these
75 studies have also demonstrated that systemic risk factors are important for the
76 prognosis of DME after PPV.[18, 24] However, to the best of our knowledge,

77 there are no reports of any specific systemic factors that can influence the
78 prognosis of DME after PPV with ILM peeling, which is a recently developed
79 advanced technique.[17] Therefore, the current study was designed to evaluate
80 potential DME prognostic factors for the best corrected visual acuity (BCVA), and
81 the foveal average retinal thickness after PPV with ILM peeling.

82

83 Materials and Methods

84 PPV with ILM peeling was performed in 37 eyes of 30 DME patients by four
85 surgeons between January 2005 and March 2008 at Nagasaki University. We
86 performed PPV with ILM peeling for cases with 0.155 or less logMAR (logarithm
87 of the minimal angle of resolution), with continuous diffuse ME more than 6
88 months, and with thicker posterior hyaloids membrane suspected. All patients
89 did not undergo panretinal photocoagulation or macular photocoagulation within
90 3 months before PPV with ILM peeling. After patient enrollment, we excluded 4
91 eyes that had no preoperative retinal thickness measurements, 1 eye with a
92 postoperative macular hole, and 1 eye in which there were no retinal thickness
93 measurements for 6 months postoperatively, resulting in a total of 31 eyes of 27
94 patients being examined in the study. None of the patients had vitreo-macular

95 traction syndrome or received any adjunctive treatment, such as anti-VEGF or
96 triamcinolone acetonide. Foveal average retinal thicknesses were determined by
97 using optical coherence tomography (OCT) (Cirrus®, Carl Zeiss Meditec, Dublin,
98 CA) to measure the central subfield mean thickness. BCVA, fundus
99 examinations, and foveal average retinal thickness before and 6 months after
100 operations were reviewed retrospectively using the patients' clinical records.

101 The relationships between preoperative systemic or ocular factors and
102 BCVA or foveal average retinal thickness before and 6 months after the
103 operation were statistically evaluated. Systemic factors examined included age,
104 sex, BMI, systolic blood pressure, hypertension, hyperlipidemia, dialysis,
105 cardiovascular disease, cerebral infarction, no diabetes treatment history until
106 diabetic retinopathy was found (no diabetes treatment), and preoperative blood
107 test results. A blood test that measured hemoglobin (Hb), hematocrit (Hct), total
108 protein (TP), albumin (alb), creatinine, blood urea nitrogen (BUN), creatinine
109 clearance (Ccr), and glycosylated hemoglobin (HbA1c) was performed 1 month
110 before surgery as the standard preoperative assessment. The ocular factors
111 examined included the type of macular edema (cystoid or not)[25, 26],
112 proliferative diabetic retinopathy (PDR), foveal hard exudates, and the presence

113 of epiretinal membrane (ERM) without fibrovascular components prior to the
114 operation. BCVA, fundus examination, and optical coherence tomography (OCT)
115 were all performed pre- and postoperatively up until 6 months after the
116 operation.

117 Statistical analysis: The results are expressed as means±standard deviation.
118 The Mann Whitney test was used to compare the BCVA and foveal average
119 retinal thickness before and after the operation. Multiple regression analysis was
120 used to evaluate BCVA and foveal average retinal thickness, which were related
121 to the above-mentioned systemic and ocular factors. Statistical analysis was
122 performed using StatFlex ver. 5.0 software. Statistical significance was set at
123 $P<0.05$.

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

126

127

128 Results

129 This study examined 31 eyes of 27 patients (7 females, 20 males; mean age
130 at operation, 59 ± 10 years). Table 1 shows the characteristics of the DME

131 patients prior to the operation. While the mean logMAR improved from 0.84 ± 0.64
132 before the operation to 0.64 ± 0.38 at 6 months after the operation, this difference
133 was not significant ($P=0.393$) (Figure 1). Foveal average retinal thickness
134 significantly improved from $473\pm146\ \mu\text{m}$ before the operation to $318\pm108\ \mu\text{m}$ 6
135 months after the operation ($P<0.0001$) (Figure 2). Table 2 shows the relationship
136 between the BCVA or foveal average retinal thickness (before and 6 months
137 after the operation), and the preoperative systemic or ocular factors. Patients
138 with cardiovascular disease or cerebral infarction ($P=0.0019$) or with cystoid
139 macular edema (CME) ($P=0.0028$) had significantly thicker preoperative foveal
140 average retinal thicknesses, while patients with ERM had a significantly lower
141 preoperative BCVA ($P=0.042$). Additionally, patients who had a higher BMI
142 ($P=0.0088$), were not on dialysis ($P=0.012$), or did not have proliferative diabetic
143 retinopathy ($P=0.013$) all exhibited a significantly thicker foveal average retinal
144 thickness at the 6-month follow-up. BCVA at the 6-month follow-up was
145 significantly lower in both the group with no diabetes treatment history until
146 diabetic retinopathy was found ($P=0.023$), and in the patients that had a higher
147 HbA1c prior to the operation ($P=0.033$). There were 19 cases that used
148 indocyanine green staining during the ILM peeling, although this was not

149 significantly correlated to the BCVA or retinal thickness. When the surgical
150 technique was examined, no statistical correlations were noted between the
151 surgeons and the BCVA or retinal thickness.

152

153 Discussion

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

163 Preoperative retinal thickness was thicker when cardiovascular disease or
164 cerebral infarction was present, while poor glycemic control resulted in lower
165 postoperative BCVA. Additionally, postoperative retinal thickness was thicker in
166 patients with a higher BMI or when they were not on dialysis. It also has been

167 reported that DME improved in conjunction with improvement of anemia[10] and
168 serum lipid levels,[14] or when patients started dialysis.[16] Studies have also
169 reported that cardiovascular disease,[13] glycemic control,[6-9, 12] and higher
170 BMI[9] were all risk factors for DR or DME. The present findings are consistent
171 with these reports, as we found ischemic disease, poor glycemic control, higher
172 BMI, and renal dysfunction to be risk factors for DME.

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

182 In summary, ocular factors such as ERM and CME were correlated with
183 both the preoperative BCVA and retinal thickness, while BCVA and retinal
184 thickness were primarily correlated with systemic factors such as no diabetes

185 treatment, HbA1c level, BMI, and dialysis, postoperatively. These results
186 additionally suggest that there is an improvement in the ocular factors after PPV
187 with ILM peeling. Even though the BCVA improvement was not statistically
188 significant in the current study, the fact that the ocular factors improved after
189 PPV is an important discovery in and by itself. Furthermore, the present data
190 indicate that improvement of systemic factors may be just as important as the
191 ocular factor improvements.

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

198 The limitations of the current study include the small number of patients and
199 the lack of any evaluation of the systemic risk factors 6 months after the
200 operation. Therefore, the possibility exists that at 6 months after the operation,
201 there was an improvement of the postoperative foveal average retinal thickness
202 due to glycemic control or positive changes in the blood test results. To clarify

203 the current results, further studies that examine larger numbers of DME cases
204 after PPV with ILM peeling will need to be undertaken.

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

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298
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300

301 Figure Legends

302

303 Figure 1. Mean logarithm of the minimum angle of resolution (LogMAR) before
304 and 6 months after pars plana vitrectomy with internal limiting membrane peeling.

305 While visual acuity improved from 0.84 ± 0.64 before the operation to 0.64 ± 0.38
306 at 6 months after the operation, this difference was not significant ($P=0.393$).

307

308 Figure 2. Mean foveal average retinal thickness before and 6 months after pars
309 plana vitrectomy with internal limiting membrane peeling. Foveal average retinal
310 thickness significantly improved from $473 \pm 146 \mu\text{m}$ preoperatively to $318 \pm 108 \mu\text{m}$
311 6 months postoperatively ($P < 0.0001$).

312 LogMAR= logarithm of the minimum angle of resolution

313

Figure 1.

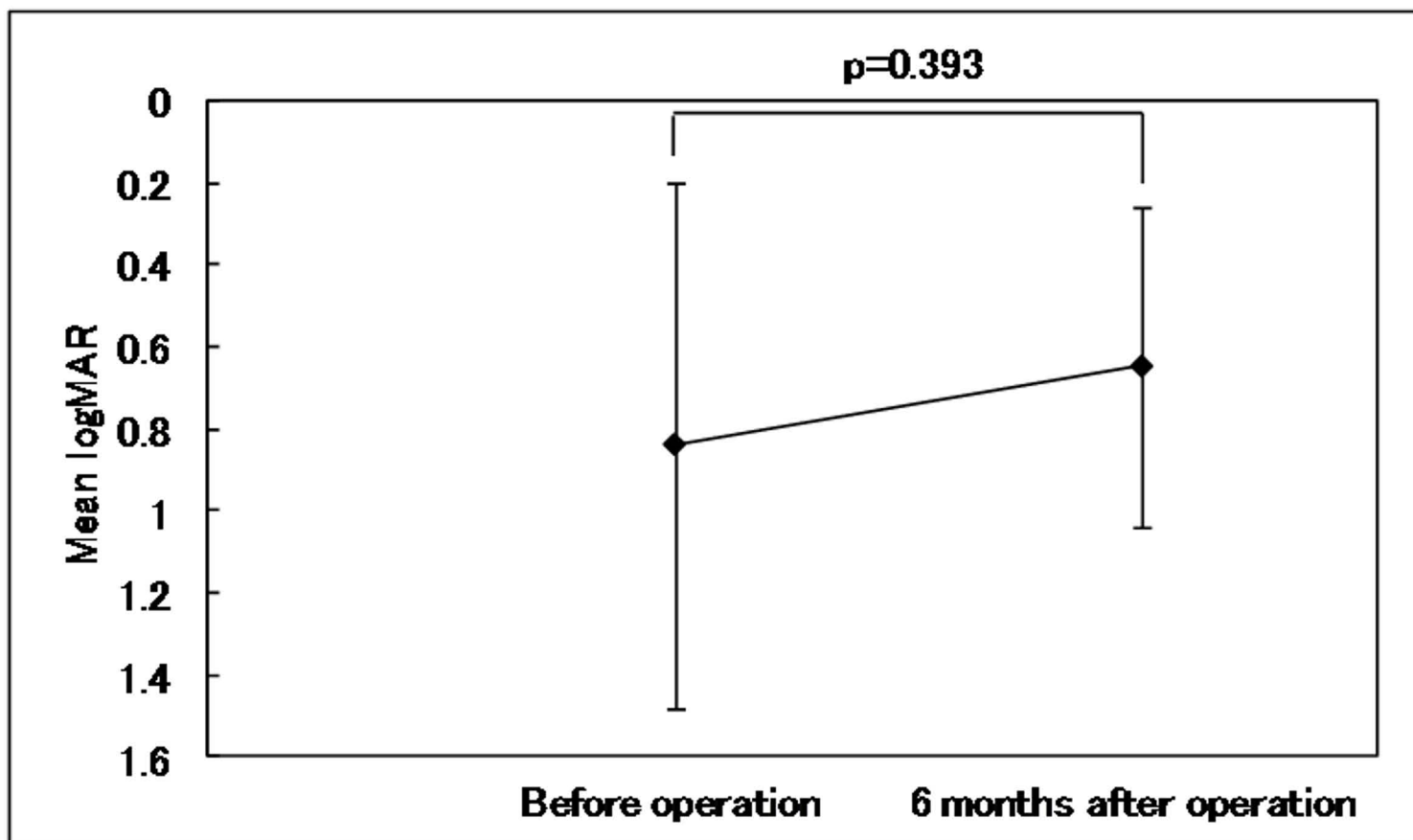


Figure 2.

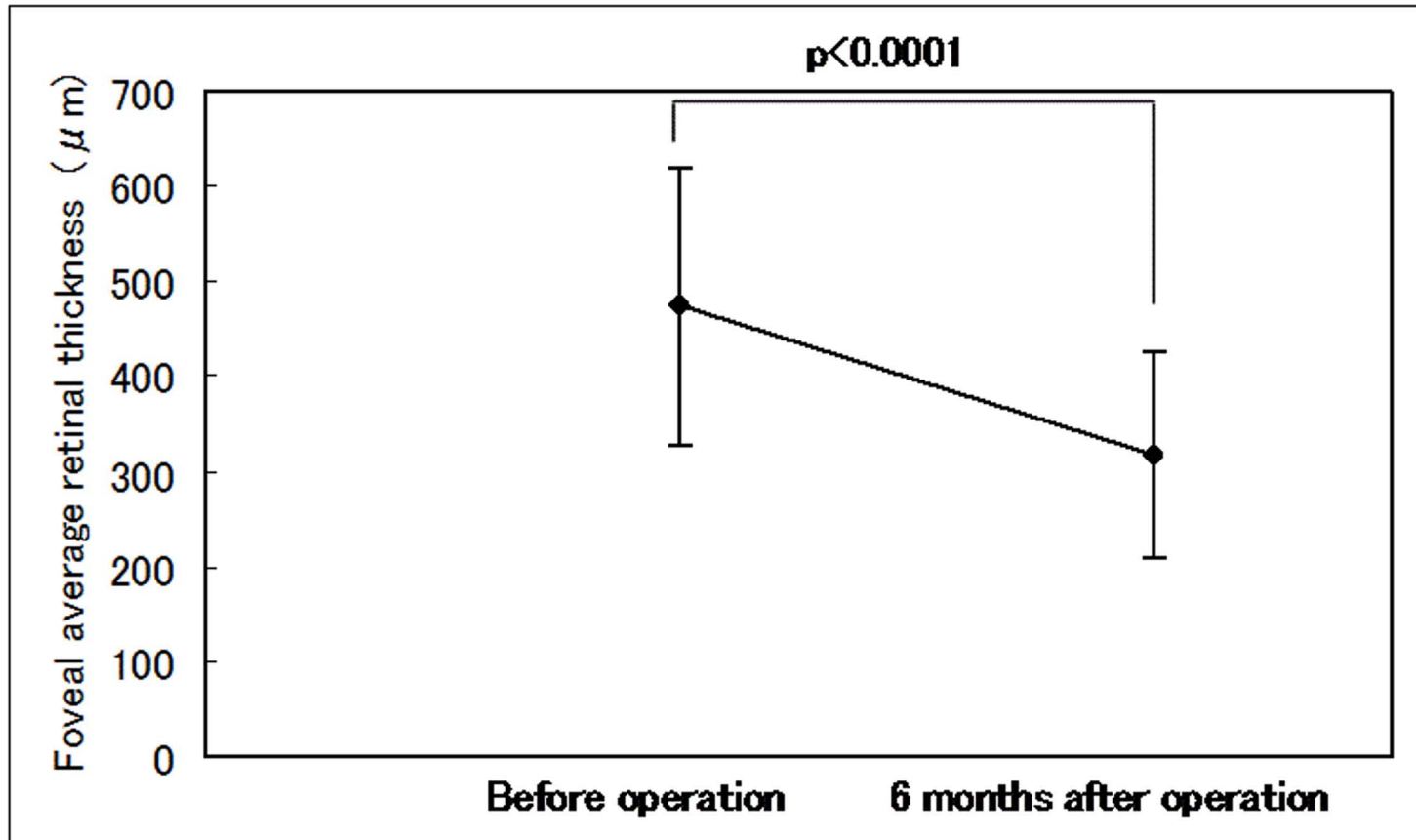


TABLE 1. Preoperative characteristics of patients with diabetic macular edema

Systemic factors	Demographics	
	Age (years) (mean±SD)	59±10
	Sex (M:F)	20:7
	Clinical	
	Body mass index (kg/m ²) (mean±SD)	23.7±2.8
	Systolic blood pressure (mmHg) (mean±SD)	137±22
	Hypertension	15
	Dialysis	3
	cardiovascular disease	4
	cerebral infarction	1
	No treatment for diabetes	17
	Blood test results (mean±SD)	
	Hemoglobin (g/dl)	12.7±1.7 (11.3-15.2)
	Hematocrit (%)	38.1±4.8 (33.4-44.9)
	Total protein (g/dl)	6.9±0.5 (6.7-8.3)
	Albumin (g/dl)	4.1±0.4 (4.0-5.0)
	Blood urea nitrogen (mg/dl)	19.2±9.1 (8-22)
	Creatinine (mg/dl)	1.25±1.56 (0.4-1.1)
	Creatinine clearance (ml/min)	82±36 (80-110)
	HbA1c (%)	7.0±1.59 (4.3-5.8)
Ocular factors	Cystoid macular edema	11
(No. of eyes)	Proliferative diabetic retinopathy	7
	Foveal hard exudates	4
	Epiretinal membrane	5

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

	Dependent factors	Independent factors	Regression coefficient	P
Preoperative	BCVA	Epiretinal membrane	-0.634	0.042
	Retinal thickness	cardiovascular disease or cerebral infarction	196.75	0.001
		Cystoid macular edema	145.06	0.002
Postoperative	BCVA	No treatment for diabetes	-0.308	0.023
		HbA1c before operation	-0.091	0.033
	Retinal thickness	Body mass index	17.44	0.008
		Dialysis	-162.63	0.012
		Proliferative diabetic retinopathy	-108.82	0.013

BCVA=best corrected visual acuity

No diabetes treatment=no history of diabetes treatment until diabetic retinopathy was found

HbA1c=glycosylated hemoglobin