MACULAR HOLE ASSOCIATED WITH AGE-RELATED MACULAR DEGENERATION

Pathogenesis and Surgical Outcomes

KYOUNG LAE KIM, MD, MS,*† JEONG MO HAN, MD, PHD,‡§ MIN SEOK KIM, MD, MS,* SANG JUN PARK, MD, PHD,* SEONG-WOO KIM, MD, PHD,¶ JAE HUI KIM, MD, PHD,** MIN KIM, MD, PHD,†† CHRISTOPHER SEUNGKYU LEE, MD, PHD,‡‡ HYUN GOO KANG, MD,†† JOO YONG LEE, MD, PHD,§§ SE JOON WOO, MD, PHD*

Purpose: To ascertain the pathogenesis of macular hole (MH) associated with age-related macular degeneration (AMD) and its surgical outcomes.

Methods: Patients with full-thickness MH associated with AMD (higher grades than intermediate) were enrolled. The mechanism of MH formation and closure rate after vitrectomy (surgical outcome) were determined using optical coherence tomography imaging.

Results: The mechanism of MH formation (35 eyes) associated with AMD was classified into four types: vitreomacular traction (42.9%), gradual retinal thinning caused by subretinal drusen or pigment epithelial detachment (22.9%), massive subretinal hemorrhage (20.0%), and combined (14.3%). In the 41 eyes that underwent vitrectomy, the logarithm of the minimum angle of resolution best-corrected visual acuity improved from 0.82 (0.10–2.30) preoperative to 0.69 (0.10–2.30) postoperative ($P = 0.001$). Successful closure of the MH was achieved in 33 eyes (80.5%) after vitrectomy. No significant association was observed between the closure rate of MH after vitrectomy and mechanism of MH formation ($P = 0.083$).

Conclusion: The mechanism of MH formation associated with AMD was classified into four types and was not related to its surgical outcome. Considering visual improvement and surgical outcome after vitrectomy in our study, active surgical treatment can be considered for MH associated with AMD.

RETINA 41:2079–2087, 2021

Age-related macular degeneration (AMD) is one of the leading causes of irreversible vision loss in people older than 50 years in the developed countries.[1] The vision-threatening complications of AMD include macular atrophy, choroidal neovascularization, retinal pigment epithelium (RPE) tear, and subretinal fibrosis.[2] The definite risk factors for the development of AMD include aging, genetic constitution of the individual, and history of smoking.[3]

Vitreomacular traction (VMT) is a suspected risk factor for the development of neovascular AMD (nAMD).[4] There are several reports about the correlation between VMT and the poor response to anti–vascular endothelial growth factor (VEGF) treatment in patients with nAMD.[5,6] In addition, VMT is a contributing factor in the macular hole (MH) development.[7] Gass et al proposed that the focal traction of the prefoveal vitreous cortex by tangential traction on the fovea might cause foveal detachment and, hence, cause MH formation.[8] Formation of MH might be contributed by the anteroposterior vitreofoveal traction as suggested by Tanner et al.[9] The majority of MH occurs as an age-related idiopathic condition.[10] Thus, both MH and AMD are age-related conditions, which become progressively worse with increasing age.

Rao et al[11] reported the prevalence and surgical outcomes of MHs in eyes with AMD by separating them as non-nAMD (nnAMD) and nAMD. According to Rao et al, the prevalence of MHs in eyes with AMD was 0.7% and the surgical outcomes of MH in nnAMD eyes were similar to those of general MH eyes, whereas it was lower in eyes with nAMD than in eyes with general MH eyes.

Additionally, there are several reports about MH in eyes with AMD.[12,13] They mainly focus on the formation of MH after anti-VEGF treatment in eyes with nAMD. However, there is limited knowledge regarding the mechanism of MH formation in eyes with AMD. Moreover, there are no reports about the differences in surgical outcomes according to the mechanism of MH formation in eyes with AMD.

Hence, the purpose of this study was to elucidate the mechanism of MH formation associated with AMD using serial optical coherence tomography (OCT) images and to analyze the surgical outcomes of MH associated with AMD after vitrectomy.

Methods

We reviewed the medical records of patients who developed full-thickness MH (FTMH) associated with AMD at five referral hospitals between January 2005 and December 2017. This study protocol was reviewed and approved by the Institutional Review Board of the Seoul National University Bundang Hospital (IRB No.: B-1808-484-110). The study adhered to the tenets of the Declaration of Helsinki.

The inclusion criteria were as follows: 1) AMD with grade higher than intermediate AMD according to the classification of the Age-Related Eye Disease Study[14] and 2) FTMH on OCT. The exclusion criteria were as follows: 1) eyes with early AMD according to the classification of Age-Related Eye Disease Study; 2) Stage 1 MH, 3) AMD occurrence after the diagnosis of MH; 3) medical history of vitreoretinal surgery for another retinal abnormality before the diagnosis of MH; and 4) other combined macular or vaso-occlusive abnormality except for AMD and MH.

The diagnosis of FTMH was performed using fundus photographs and OCT images. The OCT devices for the diagnosis of FTMH included spectral domain (Spectralis, Heidelberg Engineering, Heidelberg/Cirrus, Carl Zeiss Meditec, CA) or time domain (Stratus, Carl Zeiss Meditec, CA).

Each center collected basic demographic information of the patients, including age, gender, history of diabetes mellitus, and hypertension (HTN), on the first visit. The clinical characteristics included best-corrected visual acuity, type of AMD (dry/neovascular), and the presence of macular atrophy according to the definition of the Classification of Atrophy Meeting group.[15] Best-corrected visual acuity, OCT image, and fundus photographs were collected before and after MH formation, 6 months after MH surgery, and on the last visit. Surgical data were also collected, including history of tamponade, combined with cataract surgery. All MH surgeries were performed by pars plana vitrectomy with internal limiting membrane peeling. The tamponade material after vitrectomy was determined by the surgeon. The diagnosis of nAMD was defined by the evidence of choroidal neovascularization associated with nondrusenoid RPE detachment, serous sensory retinal detachment, subretinal hemorrhage (SRH), and/or subretinal exudation. We subdivided nAMD into three types: polypoidal choroidal vasculopathy, typical nAMD and retinal angiomatous proliferation. Polypoidal choroidal vasculopathy was diagnosed based on the presence of a branch vascular network, terminating polypoidal lesion, or both on indocyanine green angiography. Retinal angiomatous proliferation was confirmed by the evidence of retinal–retinal or retinal–choroidal anastomosis on indocyanine green angiography. The other cases were classified as typical nAMD. The MH size and stage were based on OCT findings and caliper-based function on OCT imaging as determined by the authors. The stage of MH was defined as follows; Stage 2 = FTMH $< 400\ \mu$m, Stage 3 = FTMH $> 400\ \mu$m and no vitreous separation, and Stage 4 = FTMH $> 400\ \mu$m and complete vitreous separation.[11] Anatomical surgical success was defined as the closure of MH on OCT, 6 months after MH surgery.

Statistical Analyses

The Wilcoxon signed-rank test was used to compare BCVA before and 6 months after the MH surgery. The Snellen visual acuity was converted to the logarithm of the minimum angle of resolution (LogMAR) units before comparison. The Chi-square test was used to compare the anatomical surgical success of MH surgery according to

From the *Department of Ophthalmology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Gyeonggi-do, Republic of Korea; †Department of Ophthalmology, Gangwon National University Hospital, Gangwon National University College of Medicine, Gangwon-do, Republic of Korea; ‡Department of Ophthalmology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; §Kong Eye Hospital, Seoul, Republic of Korea; ¶Department of Ophthalmology, Korea University Guro Hospital, Korea University Medicine, Seoul, Republic of Korea; **Department of Ophthalmology, Kim's Eye Hospital, Seoul, Republic of Korea; ††Department of Ophthalmology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; ‡‡Department of Ophthalmology, Institute of Vision Research, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; and §§Department of Ophthalmology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea.

Supported partially by the Bio and Medical Technology Development Program of the National Research Foundation funded by the Korean government (MSIT) (No. 2018M3A9B5021319), the NRF grant (No. 2020R1F1A1072795) and a research grant from Seoul National University Bundang Hospital (13-2019-003). The funding organization had no role in the design or conduct of this study.

None of the authors has any conflicting interests to disclose.

Reprint requests: Se Joon Woo, MD, PhD, Department of Ophthalmology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82, Gumi-ro 173beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, 13620, Republic of Korea; e-mail: sejoon1@snu.ac.kr

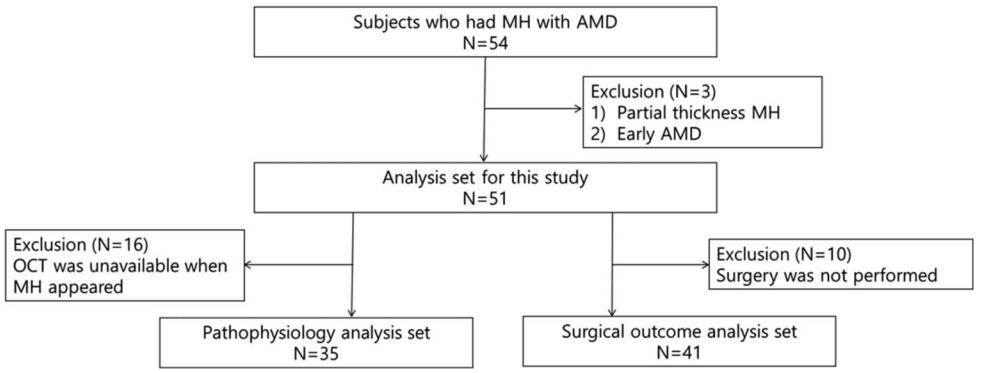

Fig. 1. Flowchart of patient selection to analyze the mechanism of FTMH formation associated with AMD and the closure rate after vitrectomy.

the type of AMD (dry/neovascular) and the mechanism of MH formation associated with AMD. Logistic regression analysis was performed to identify the factors related to the anatomical surgical success of MH surgery. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SPSS, Version 24.0 (SPSS Inc, Chicago, IL).

Results

A total of MH cases associated with AMD were included by recruiting patients from the five referral hospitals. Owing to the stage of MH and grade of AMD, three cases were excluded. Hence, 51 cases in 48 patients were included in our study for further analysis. Because of the absence of serial OCT images before the formation of MH in 16 eyes, an analysis of the mechanism of MH formation associated with AMD was performed in 35 eyes. The association between the concurrent OCT features associated with AMD and the closure rate of MH was analyzed in 41 eyes that underwent vitrectomy (Figure 1).

Among the 51 eyes (48 patients), 30 (58.8%) had dry AMD and 21 (41.2%) had nAMD. The mechanism of MH formation associated with AMD can be classified into four types using the image of OCT: VMT (29.4%) (Type A), gradual retinal thinning because of subretinal drusen or PED (15.7%) (Type B), massive SRH (13.7%) (Type C), and VMT with gradual retinal thinning because of subretinal drusen or PED (9.8%) (combined) (Figure 2). The mechanism of MH formation was undetermined in 16 eyes (31.4%) owing to the absence of OCT image at the time of MH formation. Interestingly, the preexisting large confluent drusen disappeared after the formation of MH in three of 23 eyes (13%) with dry AMD (Figure 3).

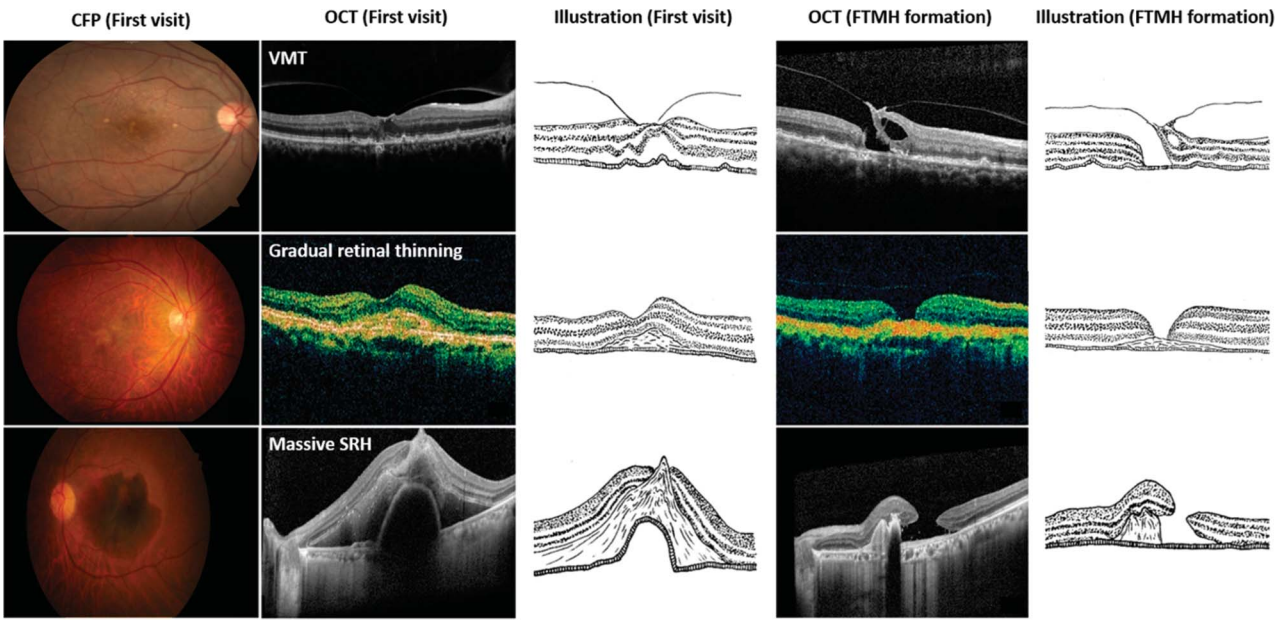

Fig. 2. Typical image of OCT and illustration at the first visit and at the time of MH formation. The classification is based on three major mechanisms according to the image of OCT: vitreomacular traction, gradual retinal thinning because of subretinal drusen or RPE detachment, massive SRH. CFP, conventional fundus photography.

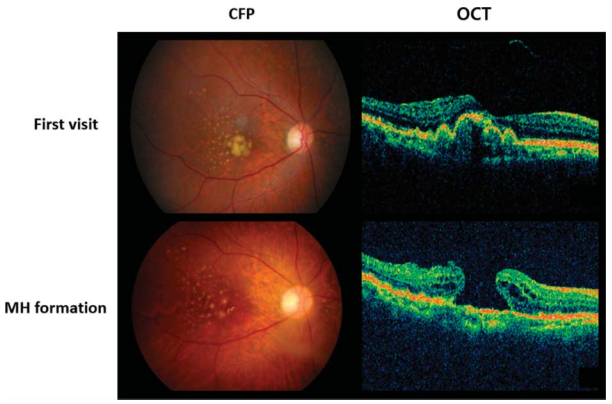

Fig. 3. Formation of a FTMH after the disappearance of large confluent drusen. CFP, conventional fundus photography.

A total of 38 patients (41 eyes) underwent vitrectomy to repair the MH associated with AMD. Among the 41 eyes, 25 (61.0%) had dry AMD and 16 (39.0%) had nAMD. The number of eyes according to the mechanism of MH formation was as follows: Type A, 12 eyes (29.3%), Type B, 7 eyes (17.1%), Type C, 4 eyes (9.8%), combined, 4 eyes (9.8%), and undetermined, 14 eyes (34.1%) (Table 1). The tamponade material after vitrectomy was as follows: sulfurhexafluoride in 16 eyes (39.0%), perfluoropropane in 19 eyes (46.3%), silicone oil in 5 eyes (12.2%), and air in 1 eye (2.4%). Among the 41 eyes, the MH size and stage could be evaluated accurately in 28 eyes using spectral-domain OCT imaging. The average size of the MH was 488.5 ± 260.4 μm. The MH stage was as follows: Stage 2, 12 eyes; Stage 3, 5 eyes; Stage 4, 11 eyes.

Among 16 eyes with nAMD and concurrent FTMH that underwent vitrectomy, polypoidal choroidal vasculopathy was observed in 5 eyes (31.3%), typical nAMD was observed in 8 eyes (50.0%), and retinal angiomatous proliferation was observed in 3 eyes (18.7%). Among the 16 eyes, 11 eyes (68.8%) were treated with intravitreal anti-VEGF injection (number of intravitreal anti-VEGF injection: 4.9 ± 2.9), 2 eyes (12.5%) were treated with photodynamic therapy, and 3 eyes (18.8%) were observed without any treatment before the development of FTMH. After vitrectomy, 8 eyes (50.0%) were treated with additional intravitreal anti-VEGF injections as a result of the recurrence of choroidal neovascularization, and 8 eyes (50.0%) were observed without any treatment (Table 2). Among 25 eyes with dry AMD and concurrent FTMH that underwent vitrectomy, 2 eyes (8.0%) were treated with intravitreal anti-VEGF injection because of neovascular change after vitrectomy.

Among 41 eyes that underwent vitrectomy to repair the MH, MH closure was observed in 33 eyes

Table 1. Demographic Information and Clinical Characteristics of Patients With FTMH Associated With AMD

Variables	Total Eyes 48 Patients	Eyes That Underwent Vitrectomy 38 Patients
Age, years (mean ± SD)	70.1 ± 7.7	69.6 ± 7.6
Gender, n (%)		
Male	19 (39.6)	18 (47.4)
Female	29 (60.4)	20 (52.6)
Underlying disease, n (%)		
Diabetes mellitus	10 (20.8)	10 (26.3)
HTN	13 (27.1)	11 (28.9)

Variables	Total Eyes 51 Eyes	Eyes That Underwent Vitrectomy 41 Eyes
Types of AMD, n (%)		
Dry	30 (58.8)	25 (61.0)
Neovascular	21 (41.2)	16 (39.0)
Mechanism of MH formation, n (%)*		
Type A	15 (29.4)	12 (29.3)
Type B	8 (15.7)	7 (17.1)
Type C	7 (13.7)	4 (9.8)
Combined	5 (9.8)	4 (9.8)
Undetermined	16 (31.4)	14 (34.1)
Follow-up period, months (mean ± SD)	66.0 ± 42.2	73.7 ± 52.3

Type A: vitreomacular traction.
Type B: gradual retinal thinning caused by subretinal drusen or RPE detachment.
Type C: massive SRH.
Combined: coexisting vitreomacular traction with gradual retinal thinning caused by subretinal drusen or RPE detachment.
*The mechanism of MH formation was determined using the serial images of OCT.

Table 2. The Clinical Characteristics of Eyes With Neovascular AMD and Concurrent FTMH That Underwent Vitrectomy

Variables	No. of Eyes
Total, n	16
Subtypes of nAMD, n (%)	
Polypoidal choroidal vasculopathy	5 (31.3)
Typical nAMD	8 (50.0)
Retinal angiomatous proliferation	3 (18.7)
Treatment for nAMD before the formation of MH, n (%)	
Photodynamic therapy	2 (12.5)
Intravitreal anti-VEGF injection	11 (68.8)
None	3 (18.8)
Additional treatment for nAMD after MH surgery, n (%)	
Intravitreal anti-VEGF injection	8 (50.0)
None	8 (50.0)

(anatomical surgical success rate: 80.5%) (Figure 4). There was no significant difference in the closure rate of MH after vitrectomy according to the type of AMD ($P = 0.698$). The closure rate of MH after vitrectomy did not show any significant difference according to the mechanism of MH formation ($P = 0.083$) (Table 3).

Logarithm of the minimum angle of resolution BCVA was significantly enhanced in 41 eyes after vitrectomy ($P = 0.001$). In eyes with dry AMD, logMAR BCVA was significantly enhanced after MH surgery ($P = 0.004$). However, no significant difference in logMAR BCVA was observed in eyes with nAMD before and after MH surgery $P = 0.136$). LogMAR BCVA was significantly enhanced in eyes with Type A mechanism of MH formation ($P = 0.013$). In contrast, for eyes with other mechanism of MH formation except for Type A, there was no significant difference in logMAR BCVA before and after vitrectomy (Table 4). There was a significant improvement in the proportion of logMAR BCVA groups (<0.1, 0.1–0.5, >0.5) after vitrectomy (<0.1, preoperative: 1/41 vs. postoperative: 2/41; 0.1–0.5, preoperative: 2/41 vs. postoperative: 10/41; >0.5, preoperative: 38/41 vs. postoperative: 29/41; $P = 0.004$) (Figure 5).

We performed logistic regression analysis to determine factors related to the closure of MH after vitrectomy (age, gender, diabetes mellitus, HTN, types of AMD [dry vs neovascular], OCT findings associated with MH formation [VMT, PED, SRF, SRH], preexisting macular atrophy cataract surgery with vitrectomy, size of MH, stage of MH, preoperative logMAR BCVA). In logistic regression analysis, preexisting macular atrophy increased the risk of failure of MH closure after vitrectomy, although it showed only marginal significance (odds ratio, 0.167; 95% confidence interval, 0.026–1.070; $P = 0.059$). However, there was no significant difference between the other factors and the closure of MH after vitrectomy (Table 5).

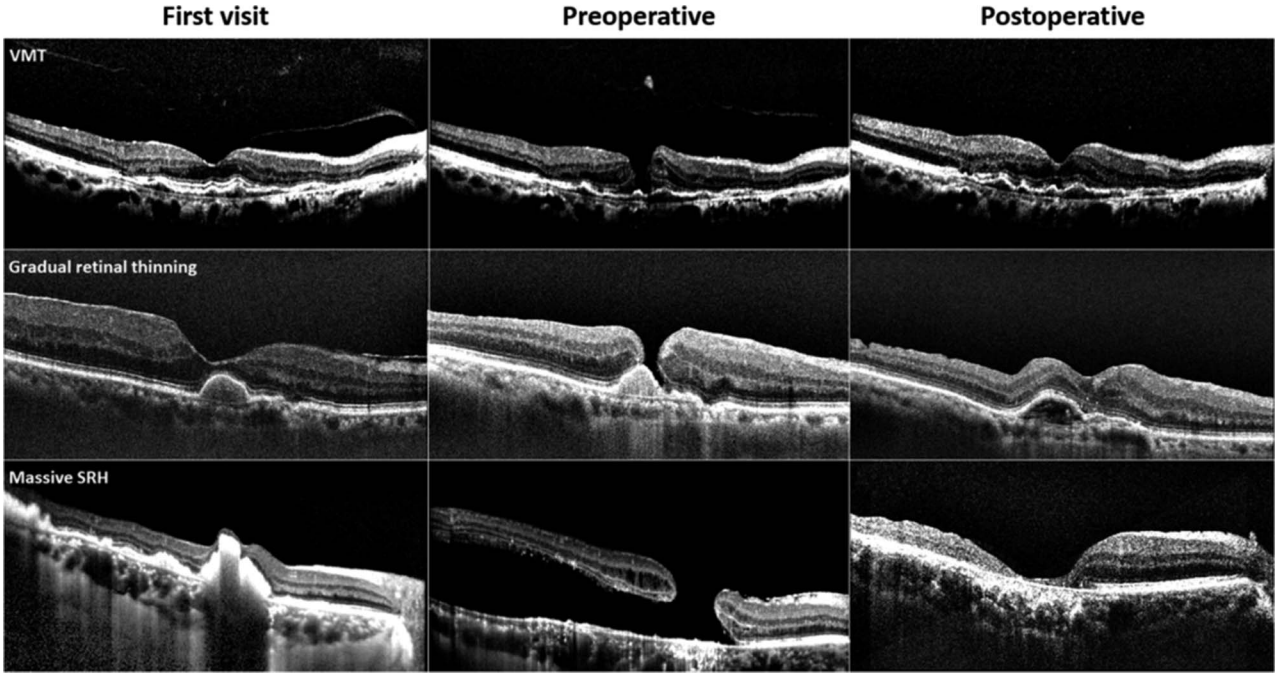

Fig. 4. Serial optical coherence tomography images of a FTMH associated with AMD at the first visit, at the time of MH formation, and 6 months after vitrectomy according to the three major mechanisms classified using OCT.

Table 3. Association of the Closure Rate of FTMH With AMD After Vitrectomy According to the Types of AMD and the Mechanism of MH Formation Classified Using OCT

	Closure Rate After Vitrectomy	P*
All	33/41 (80.5%)	
Types of AMD		0.698
Dry AMD	20/25 (80.0%)	
Neovascular AMD	3/16 (81.3%)	
Mechanism of MH formation†		0.083
Type A	11/12 (91.7%)	
Type B	7/7 (100.0%)	
Type C	3/4 (75.0%)	
Combined	4/4 (100.0%)	
Undetermined	8/14 (57.1%)	

Type A: vitreomacular traction.
Type B: gradual retinal thinning caused by subretinal drusen or RPE detachment.
Type C: massive SRH.
Combined: coexisting vitreomacular traction with gradual retinal thinning caused by subretinal drusen or RPE detachment.
Closure rate = closure of macular hole after vitrectomy (eyes)/underwent vitrectomy (eyes).
Statistical significance was defined as $P < 0.05$.
*Calculated using the Chi-square test.
†The mechanism of MH formation was determined using the serial images of OCT.

Discussion

In our study, the mechanism of MH formation associated with AMD could be classified as four types according to OCT images—VMT, gradual retinal thinning caused by subretinal drusen or PED, massive SRH, and combined (VMT with gradual thinning caused by subretinal drusen or PED). Approximately half of MH formation in AMD patients was associated with VMT, similar to idiopathic MH. The anatomical surgical success rate of MH associated with AMD was 80.5%. The logMAR BCVA improved after vitrectomy. The closure rate of MH after vitrectomy did not differ significantly according to the mechanism of MH formation. Preexisting macular atrophy increased the risk of failure after vitrectomy, although it was marginally statistically significant. However, other factors (age, gender, diabetes mellitus, HTN, type of AMD, preexisting VMT, PED, SRF, SRH on OCT, cataract surgery with vitrectomy, size of MH, stage of MH, and preoperative logMAR BCVA) were not associated with the closure rate of MH after vitrectomy.

Previous studies have reported a closure rate of idiopathic MH after vitrectomy from 78% to 96%.[16–18]

Table 4. Changes in BCVA in Eyes That Underwent Vitrectomy Because of a FTMH Associated With AMD Before and 6 Months After Vitrectomy

	Preoperative LogMAR BCVA Median (Range)	Postoperative LogMAR BCVA Median (Range)	LogMAR BCVA Change Median (Range)	P*
Total (41 eyes)	0.82 (0.10 to 2.30)	0.69 (0.10 to 2.30)	−0.18 (−0.78 to 0.60)	**0.001**
Types of AMD				
Dry	0.82 (0.10 to 1.70)	0.70 (0.10 to 1.30)	−0.19 (−0.78 to 0.30)	**0.004**
Neovascular	1.00 (0.30 to 2.30)	1.00 (0.15 to 2.30)	−0.12 (−0.60 to 0.60)	0.136
Mechanism of MH formation†				
Type A	0.91 (0.40 to 1.70)	0.52 (0.16 to 1.30)	−0.35 (−0.78 to 0.30)	**0.013**
Type B	1.00 (0.30 to 1.90)	1.00 (0.15 to 1.40)	−0.15 (−0.60 to 0.30)	0.207
Type C	2.30 (0.82 to 2.30)	1.43 (1.00 to 2.30)	−0.22 (−1.30 to 0.18)	0.285
Combined	0.76 (0.52 to 1.00)	0.50 (0.22 to 1.00)	−0.11 (−0.60 to 0.00)	0.180
Undetermined	0.81 (0.10 to 1.70)	0.85 (0.10 to 2.30)	−0.06 (−0.60 to 0.60)	0.373

Type A: vitreomacular traction.
Type B: gradual retinal thinning caused by subretinal drusen or retinal pigment epithelial detachment.
Type C: massive SRH.
Combined: co-existing vitreomacular traction with gradual retinal thinning caused by subretinal drusen or retinal pigment epithelial detachment.
Statistical significance was defined as $P < 0.05$ (bold entries).
*Calculated using Wilcoxon signed-rank test.
†The mechanism of macular hole formation was determined using the serial image of optical coherence tomography.

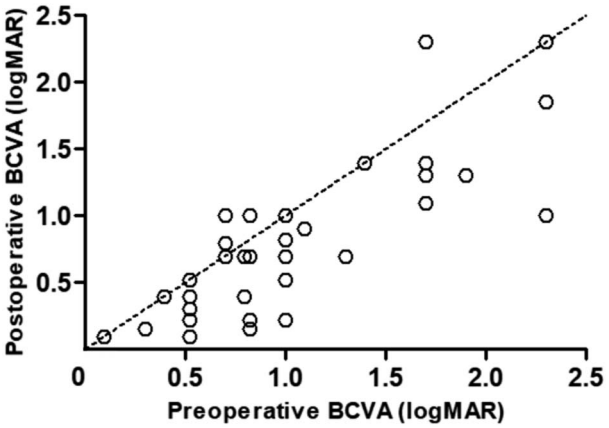

Fig. 5. Distribution of the number of eyes according to the logMAR BCVA before and after vitrectomy.

Commonly, MH occurs in the seventh decade of life and has a female predominance.[10] The age of patients in a previous study on idiopathic MH was 70.3 years, similar to that of 70.1 years in our study.[19] The proportion of women was approximately 70% in that study and 60% in our study.[19] Rao et al[11] reported that the closure rate of MH after vitrectomy was 91.5% (97/106) in eyes with dry AMD and 81.0% (17/21) in eyes with nAMD. In our study, the closure rate of MH after vitrectomy was 80.0% in eyes with dry AMD and 81.3% in eyes with nAMD. In eyes with dry AMD, the relative lower closure rate of MH after vitrectomy in our study compared with the study results of Rao et al might be because of the higher proportion of MH larger than 400 μm (39/160 [24.3%] in the study by Rao et al vs. 9/25 [36.0%] in our study). Moreover, the difference in AMD grading might have influenced the different MH closure rate between the study Rao et al and our study.

We could analyze the mechanism of MH formation associated with AMD. Vitreomacular traction has been suggested as an important cause of idiopathic MH.[20,21] There have been many reports about MH formation after anti-VEGF treatment in eyes with nAMD and VMT.[12,13,22–24] Additionally, there have been several reports about the correlation between the presence of VMT and poor response to anti-VEGF treatment in eyes with nAMD.[5,6] However, VMT may be a common risk factor for the development of AMD and idiopathic MH. In our study, VMT was observed in 16 eyes (39.0%) among 41 eyes that underwent vitrectomy. Thus, VMT can be considered as the most common cause of MH formation in eyes with AMD.

There have been several reports about MH formation in eyes with AMD.[12,13] However, they mainly

Table 5. Results of Logistic Regression Analysis on Factors for the Closure of FTMH Associated With AMD After Vitrectomy

Variables	Odds Ratio	95% CIs	*P*
Age, years	0.997	0.894–1.111	0.954
Gender (male = 0, female = 1)	0.618	0.118–3.234	0.568
Diabetes mellitus (no = 0, yes = 1)	0.381	0.041–3.546	0.397
HTN (no = 0, yes = 1)	0.889	0.151–5.241	0.896
Types of AMD (dry = 0, neovascular = 1)	0.923	0.188–4.538	0.922
OCT findings associated with MH formation			
Vitreomacular traction (no = 0, yes = 1)	5.833	0.643–52.883	0.117
Retinal pigment epithelial detachment (no = 0, yes = 1)	0.800	0.080–7.989	0.849
Subretinal fluid (no = 0, yes = 1)	0.643	0.066–6.250	0.703
Subretinal hemorrhage (no = 0, yes = 1)	0.700	0.063–7.779	0.772
Pre-existing macular atrophy (no = 0, yes = 1)	0.167	0.026–1.070	0.059
Cataract surgery with vitrectomy (no = 0, yes = 1)	0.833	0.178–3.911	0.817
Size of macular hole, μm	0.998	0.995–1.002	0.287
Stage of macular hole (stage 2 = 0, stage 3 or 4 = 1)	0.867	0.121–6.215	0.887
Preoperative logMAR BCVA	0.419	0.111–1.585	0.200

Stage 2: FTMH $<$400 μm.
Stage 3: FTMH $>$400 μm, no vitreous separation.
Stage 4: FTMH $>$400 μm, complete vitreous separation.
Statistical significance was defined as $P < 0.05$.
CIs, confidence intervals.

focused on the formation of MH after anti-VEGF treatment in eyes with nAMD. There are several hypotheses about MH formation after anti-VEGF treatment in eyes with nAMD. First, the structural changes in the vitreous body or toxicity by anti-VEGF treatment may contribute to the MH formation in eyes with nAMD.[13] Second, vitreous incarceration at the sclerotomy site for intravitreal injection may contribute to MH formation in eyes with nAMD.[13] There are several reports on MH formation in eyes with PED after anti-VEGF treatment.[10,25] Mojana et al[5] suggested that changes in PED height after anti-VEGF treatment might contribute to the formation of MH by enhancing the tractional forces. However, in eyes with PED, gradual retinal thinning by RPE dysfunction may contribute to MH formation associated with AMD. Several reports have suggested that RPE dysfunction in patients with dry AMD might contribute to MH formation by enhancing the progressive retinal thinning.[26,27] Kumar et al also suggested that the decrease in retinal thickness after anti-VEGF treatment might contribute to the formation of MH.[28] In our study, however, there were no cases in which MH developed early after anti-VEGF injections.

In our study, massive SRH was one of the major causes (13.7%) of MH formation in eyes with AMD. There are few reports about MH formation followed by SRH in eyes with AMD.[23,29] Wan et al suggested that SRH might contribute to MH formation by promoting the dehiscence of the fovea because of increased tangential pressure in the subretinal space.[29] In addition, we suspected that retinal toxicity induced by SRH might contribute to MH formation in eyes with AMD.

The logMAR BCVA was significantly enhanced after vitrectomy. The postoperative logMAR BCVA was significantly improved in eyes with dry AMD. However, there was no significant difference between pre- and postoperative BCVA in eyes with nAMD. This finding was consistent with the results of another study.[11] No visual improvement in eyes with nAMD after vitrectomy may have originated from the preexisting abnormality related to nAMD. In logistic regression analysis, preexisting macular atrophy increased the risk of failure of MH closure after vitrectomy, although it was statistically marginally significant. Thus, the lower closure rate of MH after vitrectomy in eyes with undetermined mechanism may be caused by the relatively higher rate (25%) of macular atrophy at the time of MH diagnosis (the presence of macular atrophy at the time of MH formation: Type A, 1 of 12 eyes (8.3%),; Type B, 0 of 7 eyes (0%), Type C, 0 of 4 eyes (0%), and undetermined, 4/14 eyes (28.6%)).

Our study had several limitations. First, this was a retrospective study, and a selection bias might exist related to that. Second, the mechanism of MH formation in eyes with AMD was not fully classified in all eyes because of the absence of preoperative OCT images in part of the included eyes. Third, in a previous study on atypical MHs, the presence of preoperative VMT was associated with better surgical outcomes.[7] In our study, the presence of VMT (Type A) was not associated with higher closure rate after vitrectomy (Table 3). However, the presence of VMT showed an odds ratio of 5.833 for the closure of MH without statistical significance in the logistic regression analysis ($P = 0.117$, Table 5). Therefore, the insufficient statistical power because of the small number of cases in the subgroups (mechanism of MH formation) might be the reason of failure to reveal the association between the presence of VMT and the MH closure in our study, which should be further analyzed in large-scale studies. Fourth, the OCT images that we analyzed were not homogeneous in quality, owing to the use of diverse OCT machines in different institutes. Thus, we could not accurately evaluate the size and stage of MH in all eyes. However, to the best of our knowledge, this is the first multicenter study investigating the mechanism of MH formation associated with AMD using OCT and the surgical outcome according to the mechanism.

In conclusion, MH can be caused by various mechanisms in eyes with AMD: VMT, gradual retinal thinning because of subretinal drusen or PED, and massive SRH. However, there was no significant difference in the surgical closure rate of MH according to the mechanism of MH formation. Additionally, considering visual improvement and surgical outcome after vitrectomy in our study, active surgical treatment can be considered in MH associated with AMD.

Key words: age-related macular degeneration, macular hole, mechanism, optical coherence tomography, vitrectomy.

References

1. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane database Syst Rev 2014;8:Cd005139.
2. Velez-Montoya R, Oliver SC, Olson JL, et al. Current knowledge and trends in age-related macular degeneration: genetics, epidemiology, and prevention. Retina 2014;34:423–441.
3. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. Lancet 2018;392:1147–1159.
4. Krebs I, Brannath W, Glittenberg C, et al. Posterior vitreomacular adhesion: a potential risk factor for exudative age-related macular degeneration? Am J Ophthalmol 2007;144:741–746.
5. Mojana F, Cheng L, Bartsch DU, et al. The role of abnormal vitreomacular adhesion in age-related macular degeneration: spectral optical coherence tomography and surgical results. Am J Ophthalmol 2008;146:218–227.

6. Veloso CE, Kanadani TM, Pereira FB, Nehemy MB. Vitreomacular interface after anti-vascular endothelial growth factor injections in neovascular age-related macular degeneration. Ophthalmology 2015;122:1569–1572.
7. Kumawat D, Venkatesh P, Brar AS, et al. Atypical macular holes. Retina 2019;39:1236–1264.
8. Johnson RN, Gass JD. Idiopathic macular holes. Observations, stages of formation, and implications for surgical intervention. Ophthalmology 1988;95:917–924.
9. Tanner V, Chauhan DS, Jackson TL, Williamson TH. Optical coherence tomography of the vitreoretinal interface in macular hole formation. Br J Ophthalmol 2001;85:1092–1097.
10. Ringeisen AL, Parke DW III, Dev S. Characteristics and outcomes of full-thickness macular hole repair in patients receiving anti-VEGF injections for neovascular age-related macular degeneration. Int Ophthalmol Clin 2019;59:127–135.
11. Rao P, Yonekawa Y, Abbey AM, et al. Prevalence and surgical outcomes of macular hole in eyes with age-related macular degeneration. Ophthalmol Retina 2017;1:158–164.
12. Oshima Y, Apte RS, Nakao S, et al. Full thickness macular hole case after intravitreal aflibercept treatment. BMC Ophthalmol 2015;15:30.
13. Moisseiev E, Goldstein M, Loewenstein A, Moisseiev J. Macular hole following intravitreal bevacizumab injection in choroidal neovascularization caused by age-related macular degeneration. Case Rep Ophthalmol 2010;1:36–41.
14. Ferris FL, Davis MD, Clemons TE, et al. A simplified severity scale for age-related macular degeneration: AREDS report no. 18. Arch Ophthalmol 2005;123:1570–1574.
15. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: classification of atrophy report 3. Ophthalmology 2018; 125:537–548.
16. Zhao PP, Wang S, Liu N, et al. A Review of surgical outcomes and advances for macular holes. J Ophthalmol 2018;2018:7389412.
17. Sakaguchi H, Ohji M, Oshima Y, et al. Long-term follow-up after vitrectomy to treat idiopathic full-thickness macular holes: visual acuity and macular complications. Clin Ophthalmol 2012;6:1281–1286.
18. Yamamoto K, Hori S. Long-term outcome of vitrectomy combined with internal limiting membrane peeling for idiopathic macular holes [in Japanese]. Nippon Ganka Gakkai Zasshi 2011;115:20–26.
19. Jackson TL, Donachie PH, Sparrow JM, Johnston RL. United Kingdom National Ophthalmology Database study of vitreoretinal surgery: report 2, macular hole. Ophthalmology 2013;120:629–634.
20. Johnson MW. Posterior vitreous detachment: evolution and role in macular disease. Retina 2012;32:S174–S178.
21. Sebag J. Age-related changes in human vitreous structure. Graefe Archive Clin Exp Ophthalmol 1987;225:89–93.
22. Mukherjee C, Mitra A, Kumar NA, et al. Macular hole formation after intravitreal ranibizumab injection in wet age-related macular degeneration. Open Ophthalmol J 2015;9: 177–180.
23. Regatieri CV, Duker JS. Bilateral macular hole after antivascular endothelial growth factor therapy in a patient with exudative age-related macular degeneration. Retin Cases Brief Rep 2012;6:125–128.
24. Clemens CR, Holz FG, Meyer CH. Macular hole formation in the presence of a pigment epithelial detachment after three consecutive intravitreal antivascular endothelial growth factor injections. J Ocul Pharmacol Ther 2010;26:297–299.
25. Storch MW, Hoerauf H. Case report of a secondary macular hole closure after intravitreal bevacizumab therapy in a patient with retinal pigment epithelial detachment. Indian J Ophthalmol 2017;65:632–633.
26. Duker JS, Kaiser PK, Binder S, et al. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. Ophthalmology 2013; 120:2611–2619.
27. Berinstein DM, Hassan TS, Williams GA, et al. Surgical repair of full-thickness idiopathic macular holes associated with significant macular drusen. Ophthalmology 2000;107: 2233–2239.
28. Kumar V, Shankar J. Lamellar macular hole after ranibizumab in a patient with neovascular age-related macular degeneration and vitreomacular adhesion. Retin Cases Brief Rep 2012;6: 109–110.
29. Wan MJ, Sheidow TG. Macular hole secondary to a subretinal hemorrhage. Retin Cases Brief Rep 2009;3:86–88.