Effect of 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A Reductase Inhibitors on the Meibomian Gland Morphology in Patients with Dyslipidemia

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• PURPOSE: **Previous studies have suggested an association between dyslipidemia and meibomian gland dysfunction (MGD). The aim of this prospective, nonrandomized clinical study is to evaluate the possible association of dyslipidemia and its treatment with meibomian gland (MG) morphologic changes by standardized meibography.**
• DESIGN: **Prospective, nonrandomized clinical study.**
• METHODS: **Two groups of participants were enrolled: group 1, comprised of patients under regular 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) treatment for dyslipidemia, and group 2, those with newly diagnosed dyslipidemia who were under lifestyle interventions. Meibography was performed at baseline and at both the 6- and 12-month visits and were graded by meiboscores. Participants underwent slit lamp examination for signs of changes in meibum quality and MG lid morphologic features. The Ocular Surface Disease Index questionnaire was given to measure subjective symptoms of ocular surface disease. Dry eye parameters including tear meniscus height, noninvasive first and average tear film break-up time, and Schirmer test results were also recorded.**
• RESULTS: **Ninety-eight participants completed this longitudinal study over 12 months. There were statistically significant changes in total meiboscores ($P = .01$) and upper eyelid meiboscores ($P = .012$), lid margin abnormality scores ($P = .0059$), and meibum quality ($P = .0002$) in the statin group during follow-up visits. Similar changes of upper eyelid meiboscores ($P = .046$) and meibum quality ($P = .046$) were noted in the nonstatin group.**
• CONCLUSION: **Meibomian gland atrophy and deterioration of meibum quality continued in the long term among participants with dyslipidemia even under statin usage. (Am J Ophthalmol 2020;219:240–252. © 2020 Elsevier Inc. All rights reserved.)**

MEIBOMIAN GLAND DISEASE (MGD) IS A COMMON eye disorder that is primarily caused by chronic obstruction of the meibomian glands (MGs) and qualitative/quantitative changes of the glandular secretion.[1] Globally, around 3.5%-70% of patients have MGD, with a higher prevalence in the Asian populations.[2] A prevalence rate of approximately 60% was noted among an elderly population in Taiwan.[3] If left untreated, patients may in the short term experience constant irritation and symptoms of ocular surface disease.[1] Progressive glandular atrophy and changes in eyelid margin may occur over the long term.[4]

Multiple risk factors of MGD have been noted, including age, male sex, contact lens use, menopause, androgen deficiency, benign prostatic hyperplasia, pemiphigoid, and Parkinson disease.[2,5] More recently, dyslipidemia was suggested to be an important risk factor for its modifiability and high prevalence among older adults. Previous studies have suggested that elevated total cholesterol (TC) levels were associated with moderate to severe MGD.[6,7] This association is not limited to older adults, because high cholesterol was found to be present in both young and middle-age patients with MGD.[8] Increased MGD severity was reported to be associated with increased triglyceride (TG) and low-density lipoprotein (LDL) levels.[5] Recently, increased TGs, TC, LDL, uric acid, and the presence of hepatic steatosis were found to be associated with asymptomatic MGD in a middle-aged population in Taiwan.[9] A recent population-based study regarding the prevalence and risk factors of MGD was conducted in Japan, and the results showed that there was a significant relationship between MGD and the oral intake of lipid-lowering agents.[10]

The current treatment strategies of MGD include warm compress,[11] lid hygiene,[12] preservative-free artificial tears,[13] manual gland expression of stagnant meibum,[14] topical[15] or oral antibiotics,[16,17] oral omega-3 fatty acid supplements,[18] MG probing,[19,20] and thermal pulsation.[21] However, these strategies only provide temporary relief of eye discomfort

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caused by MGD and do not provide lasting effects. 3-Hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), widely used in the treatment of dyslipidemia, are a potential lasting treatment strategy for MGD for their effectiveness in the inhibition of cholesterol synthesis and promotion of LDL uptake through hepatic LDL receptor.[22] One study examined the use of topical atorvastatin on 10 patients with dry eye and blepharitis and the results showed significant improvement.[23] However, whether the use of oral statins can slow down the progress of or alleviate MGD has not been studied.

The current study aims to address this gap by following up 2 groups of patients with dyslipidemia. One group included regular statin users while the other group relied only on lifestyle interventions (no statin use). Our hypothesis is that statin use can stabilize MGD or alleviate MGD after 12 months, as measured by meibography, morphologic lid features, meibum quality, and dry eye parameters.

METHODS

• **STUDY DESIGN:** A prospective, nonrandomized clinical study of patients with dyslipidemia was recruited over a period of 36 months (December 2016-December 2019) at National Taiwan University Hospital. Patients were initially referred to the ophthalmology clinic from the internal medicine and family medicine clinics to participate in the study. According to the treatment guidelines of dyslipidemia, the implementation of lifestyle interventions, including weight reduction, physical exercise, nutrition therapy, and smoking cessation, are important first-line treatment approaches for dyslipidemia, followed by pharmacologic intervention.[24,25] Participants were therefore divided into 2 groups: 1) the statin group, or patients undergoing regular HMG-CoA reductase inhibitor (statin) treatment for ≥12 months, and 2) the nonstatin group, or those with recently diagnosed dyslipidemia who were eligible to undergo 3-6 months of lifestyle interventions before re-evaluation for starting statin therapy. Their medical and surgical histories were collected during the initial screening period. Those with active eye infection, a history of chemical or thermal injury to the ocular surface, those who had undergone a previous operation of the eyelid or conjunctiva, those with any known allergy or contraindication to statins, those with a history of percutaneous coronary intervention, cerebrovascular accident, acute coronary syndrome, or rheumatologic diseases, and those who were taking omega-3 fatty acid supplements or were pregnant were excluded. In addition, participants in the nonstatin group were re-evaluated by their primary physicians for the necessity of initiating pharmacologic interventions every 3 months, and those who shifted to statin therapy during the follow-up period were excluded in subsequent assessments. All participants were asked to revisit every 6 months for follow-up evaluations, and new data were collected. All subjects provided written informed consent before entry into the study. This study complied with the tenets of the Declaration of Helsinki and was approved by the institutional review board of the National Taiwan University Hospital (201610044RINB). The trial was registered with ClinicalTrials.gov (identification number NCT04085016). There were few longitudinal studies on meibography and other MG parameters. For this pilot study, we based our sample size calculation on limited literature.[26-28] The sample size calculation and power analysis were assumed a type I error of 0.05, type II error of 0.8, effect size of 0.36, and power of 80%. An estimated sample size of 121 participants were required for each group. Considering a dropout rate of 10%, an estimated sample size of 134 participants was required for each group. Given that participants in the nonstatin group were re-evaluated by their primary physicians for necessity of initiating pharmacologic interventions every 3 months, those who shifted to statin therapy at the 6-month follow-up were excluded in subsequent analysis.

• **MEASURES:** *Meibography*. The upper and lower eyelids were everted and MGs were observed using noncontact meibography system (Keratograph 5M; Oculus, Wetzlar, Germany). Changes in MGs in each eyelid in terms of meiboscore were graded as: 0, no loss of MGs; 1, less than one-third loss of glands; 2, one-third to two-third loss of glands; and 3, more than two-third loss of glands. The total score of upper and lower eyelid ranged from 0-6.[27,29,30]

Meibum quality. Slit lamp examinations on the eyelid were undertaken to evaluate the meibum quality of each individual. Digital pressure was applied at the central third of the upper and lower eyelid margins to examine the ease and quality of MG expression. Clear, cloudy, granular, or toothpaste-like expression were graded as 0, 1, 2, and 3, respectively.[31-33]

Lid margin abnormality score. MG morphologic lid features were graded using lid margin abnormality score under slit lamp.[34,35] The score was calculated as the sum of the 4 signs: lid margin irregularities, telangiectasia, orifice plugging, and displacement of mucocutaneous junction, with each sign given a score of 1. Each eye received an overall score from 0 to 4, depending on the number of abnormalities.

Ocular Surface Disease Index. All participants were required to complete a standardized questionnaire about their subjective dry eye symptoms: the Ocular Surface Disease Index (OSDI).[36] The OSDI is one of the most frequently used instruments to assess ocular surface disease. This questionnaire includes 12 questions and evaluates the frequency of subjective symptoms, effects on visual function, or their relation to adverse environmental conditions over the preceding week. The

questionnaire requires approximately 5 minutes for the patient to complete, and the scores range from 0-100. On the basis of the score, symptoms of the participants can be categorized as normal (0-12), mild dry eye (13-22), moderate dry eye (23-32), or severe dry eye (33-100).[36-39]

Objective dry eye parameters. Tear meniscus height, noninvasive first tear film break-up time, and noninvasive average tear film break-up time were recorded using the Keratograph 5M (Ocular, Wetzlar, Germany). The interval between the last complete blink and the appearance of the first dry eye spot was noted as tear film break-up time. A result of <10 seconds was noted as dry eye.[40] Basic tear secretion was further measured using the Schirmer (basic secretion) test. Five minutes after instilling topical anesthetic eyedrops (Alcaine, proparacaine hydrochloride ophthalmic solution 0.5%; Alcon Laboratories, Inc, Antwerp, Belgium), the Schirmer paper strip was inserted into the lower conjunctival fornix and left in place for another 5 minutes. The wetted length (in millimeters) of the paper strip was read. Readings ≤5 mm over a period of 5 minutes were classified as dry eye.[41] Readings from 6-10 mm were classified as dry eye suspect, and those >10 mm were classified as normal.[42]

• **STATISTICAL ANALYSIS:** The baseline lipid profiles, MG, and dry eye parameters of the 2 groups were compared using the Wilcoxon rank sum test and χ^2 test. Spearman correlation was performed to reveal the correlations between MG and dry eye parameters and systemic risk factors of participants with dyslipidemia. Within-group baseline and 12-month follow-up data were compared with the Wilcoxon signed rank test. $P < .05$ was considered statistically significant. Backward stepwise regression analyses were performed to determine if MG parameters were associated with indicators of lipid profiles and demographics. In the regression models, we first used all relevant variables as independent variables (including changes in TC, LDL, high-density lipoprotein [HDL], TGs, hemoglobin A1c [HbA1c], and glucose level) and changes in MG parameters (meiboscores, meibum quality, and lid margin abnormality scores) as dependent variables. We achieved the final models with backward stepwise selection at a threshold of $P = .15$. As for the participants who dropped out or were excluded from the 12-month follow-up, their 6-month follow-up data were adopted in the statistical analysis. Statistical analysis was performed using Stata software (version 14.0; StataCorp LP, College Station, Texas, USA).

RESULTS

• **DEMOGRAPHIC AND CLINICAL DATA:** Ninety-eight participants completed the study. There were 85 participants in the statin group and 13 participants in the nonstatin group. The mean duration of statin use was 6.9 ± 4.3 years (95% confidence interval, 5.9-7.8 years) among the patients in the statin group. The 2 groups were compared in terms of age, sex, lipid profile (TGs, TC, LDL, and HDL) and glucose metabolism (HbA1c and plasma glucose) both at baseline and at the 12-month follow-up (Table 1). No statistically significant difference was noted among age and sex of the 2 groups. As for the lipid profile, mean TC and LDL levels were significantly lower in the statin group when compared with the nonstatin group ($P = .0017$ and $P = .0055$, respectively) at baseline and at the 12-month follow-up ($P = .0052$ and $P = .0074$, respectively; Table 1). There was no significant difference between the mean HbA1c level or plasma glucose between the 2 groups.

Spearman correlation analysis revealed positive correlations between age and meiboscores at baseline (including total, upper, and lower eyelids [$r_s = 0.35$, 0.27, and 0.29 and $P = .0004$, .007, and .037, respectively).

• **DISTRIBUTION OF MGD AND DRY EYE AT BASELINE:** There were no statistically significant differences in baseline MG parameters between the statin and the nonstatin groups (Table 2). The criteria for diagnosis of MGD were based on the following: 1) lid margin abnormality scores ≥2; 2) the presence of MG orifice plugging; and 3) cloudy, granular, or toothpaste-like meibum expression (meibum quality, ≥1).[10,34] There were 40% (34/85) of participants with MGD in the statin group and 38.5% (5/13) in the nonstatin group. No statistically significant difference was found in the ratio of MGD between the 2 groups ($P = .96$).

On the other hand, the baseline distribution of dry eye parameters was described in Table 3. No statistically significant between-group difference was noted. Most of our participants had mild to moderate dry eye. Around 50% of the participants in both groups (36 of the statin group and 6 of the nonstatin group) had symptoms of dry eye according to OSDI scores (Table 3). According to the Schirmer test results, 39 patients (47.6%) in the statin group and 6 patients (46.5%) in the nonstatin group belonged to dry eye suspect, while 27 patients (32.9%) of the statin group and 4 patients (30.8%) in the nonstatin group had dry eye. Under the category of noninvasive first tear film break-up time, the distribution of mild to moderate dry eye seemed to vary between the 2 groups. There was 40% of mild to moderate dry eye in the statin group and 16.7% in the nonstatin group. On the other hand, the distribution of mild to moderate dry eye was similar between the 2 groups under the category of noninvasive average tear film break-up time (32.9% of the statin group vs 33.3% of the nonstatin group). Reduced tear meniscus height (<0.25 mm) was noted in both groups, with most participants belonging to the dry eye suspect subcategory. By using χ^2 tests, we found that there was no significant association between the distribution of dry eye and the study groups under each of the categories of

TABLE 1. Demographic Characteristics, Lipid Profiles, and Blood Glucose Levels of the Statin and Nonstatin Groups at Baseline and at 12 Months of Follow-Up

	Mean (SD)		
	Statin	Nonstatin	*P* Value[a]
Participants, *n*	85	13	
Male, *n* (%)	26 (30.6)	5 (38.5)	.57
Age	67.0 (10.7)	69.5 (6.73)	.46
Diabetes, *n* (%)	62 (72.9)	8 (61.5)	.63
Baseline			
TC (mg/dL)	183.9 (43.7)	214.3 (13.5)	.0017[b]
LDL (mg/dL)	105.8 (33.2)	128.7 (20.8)	.0055[b]
HDL (mg/dL)	50.8 (14.1)	55.7 (15.5)	.36
TG (mg/dL)	135.2 (46.4)	121.5 (55.0)	.28
HbA1c (%)	7.1 (1.4)	7.0 (0.8)	.48
Fasting glucose (mg/dL)	130.2 (34.9)	135.3 (31.9)	.9
Postprandial glucose (mg/dL)	185.2 (62.8)	203.0 (34.3)	.49
Follow-up			
TC (mg/dL)	175.7 (5.4)	200.9 (4.2)	.0052[b]
LDL (mg/dL)	99.3 (3.5)	119.4 (4.7)	.0074[b]
HDL (mg/dL)	51.8 (2.7)	52.8 (4.1)	.7
TG (mg/dL)	145.2 (7.8)	112.4 (11.5)	.12
HbA1c (%)	6.9 (0.1)	6.6 (0.3)	.61
Fasting glucose (mg/dL)	127.1 (3.8)	122.1 (9.3)	.56
Postprandial glucose (mg/dL)	177.9 (14.2)	157.5 (3.5)	.96

HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation; TC = total cholesterol; TG = triglyceride.

[a]*P* values based on χ^2 and Wilcoxon rank sum tests.

[b]Statistically significant ($P < .05$).

TABLE 2. Comparison of the Baseline Meibomian Gland Parameters Between the Statin and Nonstatin Groups

	Mean (SD)		
Parameters (Baseline)	Statin	Nonstatin	*P* Value[a]
Total meiboscore	2.81 (1.37)	3.25 (1.66)	.47
Meiboscore, upper eyelid	1.58 (0.8)	1.5 (0.8)	.62
Meiboscore, lower eyelid	1.24 (0.9)	1.75 (0.97)	.079
Meibum quality	1.05 (0.36)	1.25 (0.45)	.14
Lid margin abnormality score	1.75 (1.9)	2.18 (1.17)	.41
Lid margin irregularity	0.13 (0.34)	0.33 (0.49)	.12
Telangiectasia	0.47 (0.50)	0.50 (0.52)	.93
Plugging	0.83 (0.38)	0.38 (0.39)	.94
Displacement of mucocutaneous junction	0.32 (0.47)	0.45 (0.52)	.53

SD = standard deviation.

[a]Based on the Wilcoxon rank sum test.

OSDI, Schirmer test, noninvasive first and average tear film break-up time, and tear meniscus height ($P > .05$).

Based on the Schirmer test results, 12 of 27 (44.4%) participants with dry eye were diagnosed with MGD and 12 of 34 (35.3%) participants with MGD had dry eye in the statin group. As for the nonstatin group, 2 of 4 (50%) participants with dry eye were diagnosed with MGD and 2 of 5 (40%) participants with MGD had dry eye.

TABLE 3. Distribution of the Subjective and Objective Dry Eye Parameters of the Statin and Nonstatin Groups at Baseline

Dry Eye Parameters	Statin	Nonstatin	*P* Value[a]
OSDI			
Mean (95% CI)	17.3 (13.3-21.4)	21.9 (7.7-36.0)	.82
Normal (0-12), *n* (%)	36 (50.0)	7 (53.9)	
Mild to moderate (13-32), *n* (%)	25 (44.7)	2 (15.3)	
Severe (33-100), *n* (%)	11 (15.3)	4 (30.8)	
Schirmer test (millimeter/5 minutes)			
Mean (95% CI)	7.6 (6.0-8.6)	8.8 (4.6-13.0)	.77
Normal (>10), *n* (%)	16 (19.5)	3 (23.1)	
Dry eye suspect (6-10), *n* (%)	39 (47.6)	6 (46.5)	
Dry eye (≤5), *n* (%)	27 (32.9)	4 (30.8)	
Noninvasive first tear film break-up time (seconds)			
Mean (95% CI)	8.2 (6.9-9.4)	7.5 (3.5-11.6)	.51
Normal (>10), *n* (%)	20 (23.5)	4 (33.3)	
Mild to moderate (5-10), *n* (%)	34 (40.0)	2 (16.7)	
Severe (≤5), *n* (%)	31 (36.5)	6 (50.0)	
Noninvasive average tear film break-up time (seconds)			
Mean (95% CI)	10.7 (9.4-12.0)	10.7 (6.2-15.2)	.81
Normal (>10), *n* (%)	41 (48.2)	5 (41.7)	
Mild to moderate (5-10), *n* (%)	28 (32.9)	4 (33.3)	
Severe (≤5), *n* (%)	16 (18.8)	3 (25.0)	
Tear meniscus height (millimeters)			
Mean (95% CI)	0.19 (0.17-0.21)	0.24 (0.11-0.37)	.69
Normal (>0.25), *n* (%)	16 (18.8)	2 (16.7)	
Dry eye suspect (0.1-0.25), *n* (%)	56 (65.9)	9 (75.0)	
Dry eye (<0.1), *n* (%)	13 (15.3)	1 (8.3)	

CI = confidence interval; OSDI = Ocular Surface Disease Index.
[a]Based on the Wilcoxon rank sum test.

• **LONGITUDINAL CHANGES IN MG AMONG PARTICIPANTS WITH DYSLIPIDEMIA:** Lipid levels of the statin group remained stationary during the 12-month follow-up. There was significant decrease in TC ($P = .0075$) and LDL ($P = .012$) levels in the nonstatin group in the follow-up visit. There was no significant difference between the baseline and follow-up HbA1c and blood glucose levels (Table 4).

Within-group analysis of the baseline and 12-month follow-up data showed that there were minimal but significant changes in the meiboscores in both statin and nonstatin groups based on the Wilcoxon signed rank test (Table 5). Statistically significant differences were detected in total meiboscores ($P = .01$) and upper eyelid meiboscores ($P = .012$) between the baseline and follow-up visits in the statin group (Figure 1).[43] Moreover, there was significant deterioration in meibum quality ($P = .0002$) and lid margin abnormality scores in the statin group ($P = .0059$; Table 5).

Backward stepwise regression models of MG parameters revealed that changes in total meiboscores were associated with HDL ($P = .04$) and HbA1c levels ($P = .001$) for the follow-up changes in the statin group (Table 6). In addition, changes in lid margin abnormality scores was positively associated with HDL ($P = .002$) and TG ($P = .004$; Table 6).

On the other hand, similar results were observed in the nonstatin group. Statistically significant deterioration of the upper eyelid meiboscores ($P = .046$) and meibum quality ($P = .046$) were noted in the follow-up visits despite improved TC and LDL levels in the nonstatin group (Table 5).

Progression of total meibscores occurred in 19 (24.4%) of the statin group (Fig. 1) while most of them remained stationary (Fig. 2). On the other hand, progression of total meibscores occurred in 2 (16.7%) of the nonstatin group (Fig. 3) with the rest being stationary (Fig. 4). No significant difference in the rate of progression was noted between the 2 groups ($P = .912$).

• **LONGITUDINAL CHANGES IN DRY EYE PARAMETERS AMONG PARTICIPANTS WITH DYSLIPIDEMIA:** Spearman correlation analysis of the statin group with lipid levels at baseline revealed positive correlation between OSDI score and TG level ($r_s = 0.48$, $P < .001$; Table 7). Schirmer test

TABLE 4. Comparison of the Baseline and Follow-Up Lipid Profile, HbA1c, and Blood Glucose Level

Parameters	Group	Mean (SD)		*P* Value[a]
		Baseline	Follow-Up	
TC (mg/dL)	Statin	183.9 (43.7)	175.7 (5.4)	.52
	Nonstatin	214.3 (13.5)	200.9 (4.2)	.0075[b]
LDL (mg/dL)	Statin	105.8 (33.2)	99.3 (3.5)	.13
	Nonstatin	128.7 (20.8)	119.4 (4.7)	.012[b]
HDL (mg/dL)	Statin	50.8 (14.1)	51.8 (2.7)	.50
	Nonstatin	55.7 (15.5)	52.8 (4.1)	.05
TG (mg/dL)	Statin	135.2 (46.4)	145.2 (7.8)	.29
	Nonstatin	121.5 (55.0)	112.4 (11.5)	.86
HbA1c (%)	Statin	7.1(1.4)	6.9 (0.1)	.75
	Nonstatin	7.0 (0.8)	6.6 (0.3)	.27
Fasting glucose (mg/dL)	Statin	130.2 (34.9)	127.1 (3.8)	.26
	Nonstatin	135.3 (31.9)	122.1 (9.3)	.15
Postprandial glucose (mg/dL)	Statin	185.2 (62.8)	177.9 (14.2)	.77
	Nonstatin	203 (34.3)	157.5 (3.5)	.18

HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation; TC = total cholesterol; TG = triglyceride.

[a]Within-group comparison. *P* values based on Wilcoxon signed rank test.

[b]Statistically significant ($P < .05$).

of the statin group was positively correlated with HDL level at baseline ($r_s = 0.31$, $P = 0.01$; Table 7). Noninvasive first and average tear film break-up time was negatively correlated with age ($r_s = -0.27$, $P = .01$, and $r_s = -0.2$, $P = .007$, respectively). Noninvasive first tear film break-up time was positively correlated with average tear film break-up time ($r_s = 0.86$, $P < .0001$) and tear meniscus height ($r_s = 0.23$, $P = .032$). Schirmer test value, however, was not significantly associated with tear meniscus height ($P > .05$). There was no significant difference between the baseline and follow-up OSDI score, Schirmer test, tear meniscus height, and noninvasive first and average tear film break-up time ($P > .05$; Table 8).

DISCUSSION

IT IS WELL KNOWN IN THE LITERATURE THAT MGD IS ASSOciated with an abnormal lipid profile.[6-9] However, there has been no meibography study on this topic before. Previous studies were epidemiologic and focused on the possible association of MGD with an unrecognized abnormal lipid profile. The diagnosis of MGD was based on clinical grading of glandular obstruction and meibum quality.[5-9] Our study differs from the former studies such that we attempted to identify the structural change in MG among patients already diagnosed with dyslipidemia, so as to gain a better insight of the possible pathophysiology of the disease.

While the great majority of participants had stable meiboscores, our results showed that the use of statins did not halt the progression of MG dropout. Longitudinal observation revealed a statistically significant increase in total and upper eyelid meiboscores, as well as lid margin abnormality scores in the statin group. Our results were in agreement with the recently published literature where significant association was found between MGD and oral lipid-lowering agent intake.[10] Improvement in lipid level in the nonstatin group also failed to stabilize or alleviate the severity of MGD. One possible explanation was the progressive atrophy effect induced by dyslipidemia. We speculate that MG atrophy continued to progress despite a stationary lipid profile in participants with or without statin use. Meibum of abnormal quality continued to stagnate in the MGs, resulting in ductal dilatation, orifice plugging, and MG loss.[44] This idea is supported by the same trend observed in the upper meiboscores of the nonstatin group.

In addition, lid margin abnormality scores continued to decline in both groups and was found to be associated with HDL and TG levels in our regression models. The results were in accordance with previous studies where increased TGs, HDL, and LDL associated with increasing severity of stage of MGD.[6,8,45] The role of HDL in MGD was also explored by Kurikose and associates[46] in their review article. Though HDL was considered cardioprotective, it was shown to enhance TG and cholesterol concentrations during sebaceous epithelial cell differentiation in animal models.

TABLE 5. Mean and Standard Deviations of Baseline and Follow-Up Meiboscores, Meibum Quality, and Meibomian Gland Lid Features in Statin and Nonstatin Groups

Parameters	Statin, Mean (SD)			Nonstatin, Mean (SD)		
	Baseline	Follow-Up	*P* Value	Baseline	Follow-Up	*P* Value
Total meiboscore	2.82 (1.37)	3.0 (1.41)	.01[a]	3.25 (1.66)	3.42 (1.73)	.16
Meiboscore, upper eyelid	1.58 (0.8)	1.71 (0.79)	.012[a]	1.5 (0.8)	1.83 (0.83)	.046[a]
Meiboscore, lower eyelid	1.24 (0.9)	1.29 (0.85)	.29	1.75 (0.97)	1.58 (1.08)	.16
Meibum quality	1.05 (0.36)	1.32 (0.47)	.0002[a]	1.25 (0.45)	1.58 (1.08)	.046[a]
Lid margin abnormality score	1.75 (1.19)	2.13 (0.93)	.0059[a]	2.18 (1.17)	2.18 (1.17)	1.0
Lid margin irregularity	0.13 (0.34)	0.04 (0.20)	.02[a]	0.33 (0.49)	0.17 (0.39)	.16
Telangiectasia	0.47 (0.50)	0.66 (0.48)	.013[a]	0.50 (0.52)	0.58 (0.51)	.65
Plugging	0.83 (0.38)	0.96 (0.20)	.0039[a]	0.83 (0.39)	1.0 (0)	.16
Displacement of mucocutaneous junction	0.32 (0.47)	0.47 (0.50)	.029[a]	0.45 (0.52)	0.55 (0.52)	.65

SD = standard deviation.
[a]Statistically significant ($P < .05$).

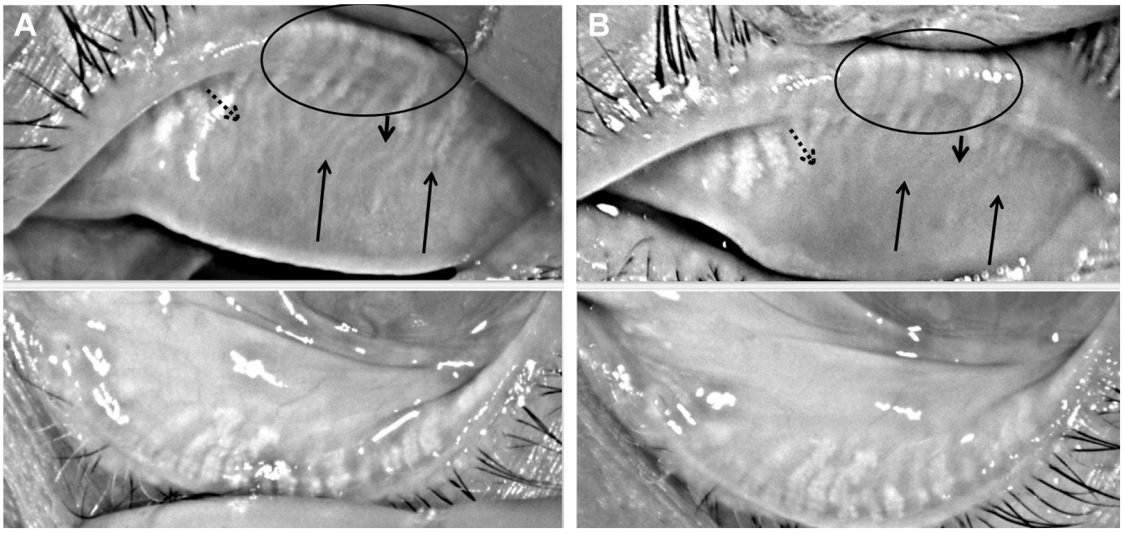

FIGURE 1. Representative meibography image of statin group with progressive meibomian gland atrophy. (A) Baseline image of upper eyelid with meiboscore of 1 and lower eyelid with meiboscore of 2 (total meiboscore = 3). Note the obstructed and thickened meibomian glands near the orifice (circled) and thinning of the proximal meibomian glands in the middle of the upper eyelid (long arrows). (B) Twelve-month follow-up image showed progressive obstruction near the orifice (circled). There were shortening (dotted arrows) and dropout of the slender glands (long arrows). Note the atrophy of meibomian gland proximal to the obstructed gland (short arrows). There was no change in the lower eyelid meiboscore, but the meiboscores of upper eyelid progressed to grade 2 (total meibscore = 4).

In our study, MG morphology and function became worse, but tear film stability seemed to be stable. A possible explanation is that OSDI score was correlated with TG, which remained stationary during the study period. Similarly, Schirmer tests were positively associated with HDL, which had no significant change within the study period. On the other hand, statistical analysis showed that noninvasive tear film breakup time did not correlate with blood lipid level (Table 7). Tear film breakup time was shown to be associated with tear meniscus height. Despite worsening of MG morphology or meibum quality, the noninvasive tear film break-up time did not have significant changes. This might imply that either the tear film stability was maintained by the compensatory mechanism of aqueous secretion, or MGD might not be the only predictor for noninvasive tear film break-up time. Apart from the

TABLE 6. Backward Stepwise Regression Model for Predicting the Changes in Ocular Parameters

Outcome	Predictor	*B*	SE	*t*	*P* Value	Adjusted R^2	F
Total meiboscore	HDL	0.023	0.011	2.18	.04[a]	0.43	9.89[b]
	HbA1c	0.39	0.095	4.06	.001[a]		
	Constant	0.20	0.095	2.15	.043[a]		
			LDL was removed due to $P = .64 > .15$				
Meibum quality	Constant	0.21	0.10	2.01	.057	—	—
			LDL was removed due to $P = .53 > .15$				
Lid margin abnormality scores	Age	−0.071	0.038	−1.86	.08	0.33	2.88[b]
	HDL	0.13	0.037	3.57	.002[a]		
	LDL	0.085	0.043	1.99	.063		
	TC	−0.069	0.037	−1.86	.081		
	TG	0.033	0.0098	3.35	.004[a]		
	Fasting glucose	−0.012	0.0075	−1.56	.14		
	Constant	5.08	2.66	1.91	.073		

HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SE = standard error; TC = total cholesterol; TG = triglyceride.

Regression models were constructed based on backward stepwise selection at a threshold of $P = .15$.

[a]Statistically significant ($P < .05$).

[b]Model $P < .05$.

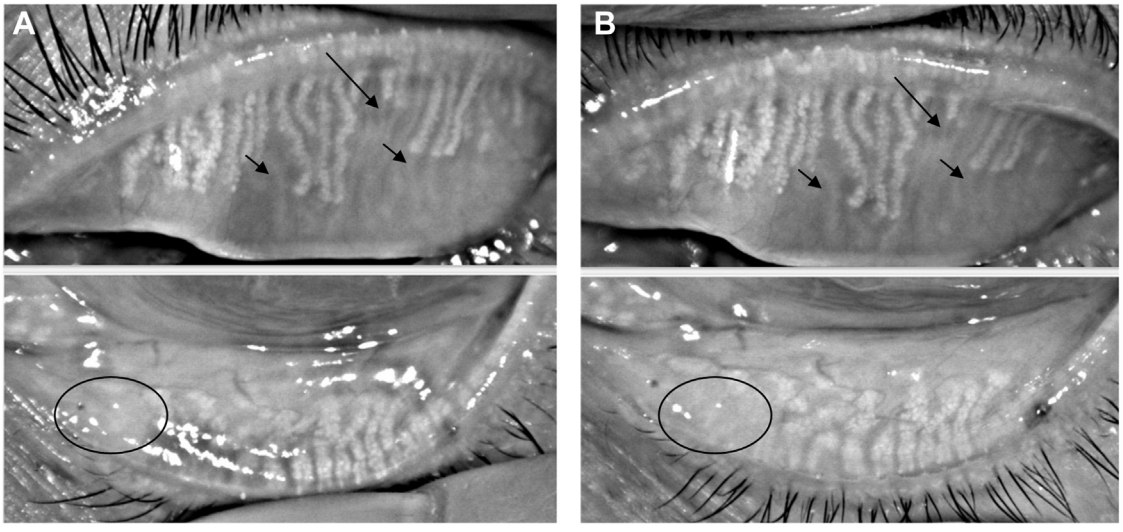

FIGURE 2. Meibography of meibomian gland morphology in the statin group. The (A) baseline and (B) 12-month follow-up images showed partial loss of meibomian glands of upper eyelid (grade 2) and lower eyelid (grade 1), with a total meiboscore of 3. The meiboscores remained stationary at the follow-up period. Tadpole-like gland atrophy was noted proximal to obstructed gland (long arrows). Shadows of attenuated glands formed ghost images (short arrows) on the upper eyelid meibography. There were fluffy areas (circled) with no clear glandular structure on the lower eyelid.[43]

lipid layer of the tear film that prevents evaporation there was evidence showing that tear film break-up time was also related to mucin production.[47] Although a strong relationship between dyslipidemia and dry eye has been reported,[48] our results suggest that treatment of dyslipidemia might not reverse the underlying dry eye conditions. This coincides with the presentation of more severe dry eye symptoms among participants of the Blue Mountains Eye Study III with regular oral statin usage.[49]

In addition, previous studies addressed the role of aging in MG changes.[27,50-52] In molecular level, the acinar apoptotic pathway must be altered to stop MGD from progression. A solution to MGD might require an antiaging modality. A series of studies by Butovich[53]

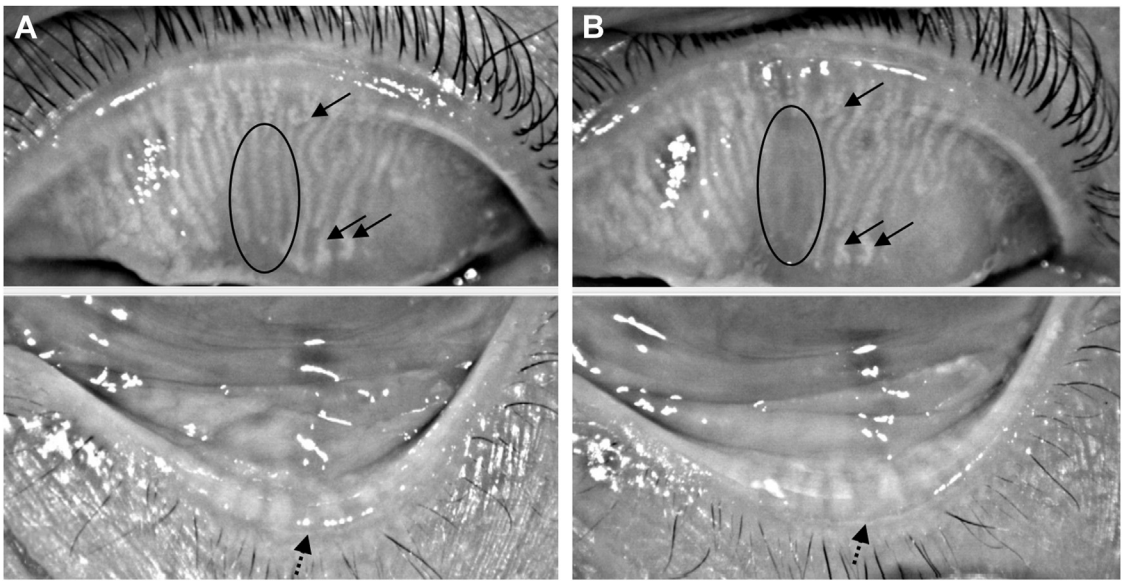

FIGURE 3. Representative meibography image of the nonstatin group with progressive meibomian gland atrophy. (A) Baseline image of the upper eyelid with a meiboscore of 1 (less than one-third loss) and the lower eyelid with a meiboscore of 2 (more than one-third loss). The total meiboscore grade was 3. (B) Meibomian glands appeared hooked and distorted (solid arrows). There was progressive atrophy (circled) in the upper eyelid at follow-up period (meiboscore progressed to 2 in the upper eyelid).

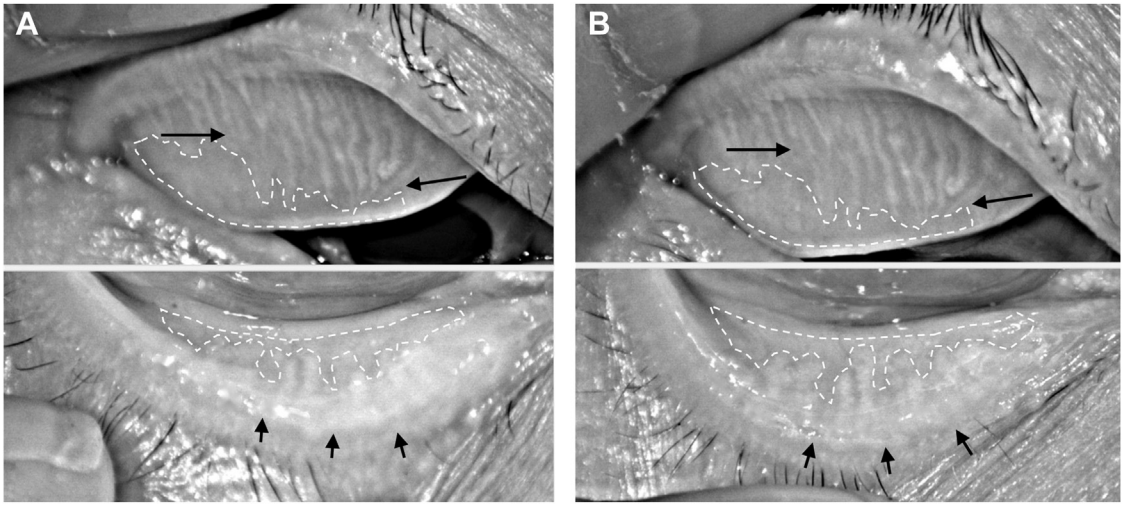

FIGURE 4. Stationary meibomian gland morphology of the nonstatin group at (A) baseline and (B) 12-months of follow-up. There was more than one-third loss of glands in both the upper and lower eyelids. The meiboscore was 2 in the upper eyelid and 2 in the lower eyelid, with a total meiboscore of 4. The meibomian glands appeared thin and tapered toward the proximal upper eyelid (long arrows). In the lower eyelid, gland shortening and dropout are indicated with short arrows.

proposed in situ meibogenesis in human tarsal plates. Previously studied bioavailability of statin ranges from 5%-80%, depending on different pharmacokinetic properties of individual statins.[54] Depending on the bioavailability of statin therapy, oral medications might not have adequate penetration into tarsal plates of patients with MGD. In addition, taking into account in situ meibogenesis, it remains an open question whether decreased plasma cholesterol would stimulate or inhibit cholesterol or cholesteryl ester synthesis in MGs. The alteration of meibum lipid subtype ratios by statins might be harmful to MG. Further lipidomics study is required to confirm the pharmacologic effect of statins on various meibum components.

TABLE 7. Correlations of Dry Eye Parameters of Statin Group with Lipid Levels at Baseline

	OSDI		Schirmer Test		Noninvasive First TBUT		Noninvasive Average TBUT		Tear Meniscus Height	
	r_s	*P* Value	r_s	*P* Value	r_s	*P* Value	r_s	*P* Value	r_s	*P* Value
Age	−0.03	NS	0.07	NS	−0.27	.01[a]	−0.20	.007[a]	0.07	NS
Sex	−0.06	NS	−0.12	NS	0.09	NS	0.10	NS	0.12	NS
TG	0.48	<.001[a]	−0.13	NS	0.08	NS	0.10	NS	0.03	NS
TC	0.13	NS	0.14	NS	−0.09	NS	0.002	NS	0.04	NS
LDL	0.10	NS	0.10	NS	0.01	NS	0.01	NS	0.86	NS
HDL	−0.05	NS	0.31	.01[a]	−0.12	NS	0.01	NS	0.04	NS

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant; OSDI = Ocular Surface Disease Index; r_s = Spearman correlation coefficient; TBUT = tear film break-up time; TC = total cholesterol; TG = triglyceride.

[a]Statistically significant ($P < .05$).

TABLE 8. Comparison of Dry Eye Parameters Between Baseline and Follow-Up Period

Parameters	Group	Mean (SD)		*P* Value[a]
		Baseline	Follow-Up	
Ocular Surface Disease Index	Statin	18.1 (18.6)	20.0 (19.6)	.16
	Nonstatin	18.9 (32.8)	23.4 (19.3)	.59
Schirmer test (millimeters/5 minutes)	Statin	5.5 (1.0)	4.1 (1.7)	.20
	Nonstatin	8.5 (2.1)	6.0 (2.8)	.18
Noninvasive first tear film break-up time (seconds)	Statin	8.0 (5.5)	8.2 (6.1)	.71
	Nonstatin	7.5 (6.4)	9.6 (7.0)	.56
Noninvasive average tear film break-up time (seconds)	Statin	10.7 (5.6)	10.9 (6.0)	.85
	Nonstatin	10.7 (7.1)	12.7 (7.9)	.69
Tear meniscus height (millimeters)	Statin	0.2 (0.1)	0.2 (0.1)	.053
	Nonstatin	0.2 (0.2)	0.3 (0.2)	.14

SD = standard deviation.

[a]Based on the Wilcoxon signed rank test.

There was significant decrease in TC and LDL levels of the nonstatin group in the follow-up visit. A hypothesis for this is that the statin group consisted of participants with long-term, well-controlled dyslipidemia while the nonstatin group were recently diagnosed and relatively short-term. Contrary to the relatively stable lipid profile of the statin group, there was more potential of improvement in the recently diagnosed nonstatin group. Our regression models showed that meiboscores and lid margin abnormality scores correlated not only with lipid profile but also with glucose metabolism. One possible explanation was the molecular interchangeability of lipid and glucose.[9] Increase in the frequency of MG obstruction and meibum quality in patients with type 2 diabetes was reported in the literature.[55] The diabetic group was found to have more MG dropout and higher meiboscores than the control group.[56,57] Dyslipidemia is a common comorbidity of diabetes.[58,59] It is possible that morphology and functional change of MGs could be affected by both dyslipidemia and diabetes. However, the percentage of diabetes between the 2 groups of participants was similar (Table 1). This enabled us to evaluate whether statin use could prohibit the MGs from morphologic and functional change. By controlling the effect of diabetes through multiple regression, our stepwise regression model showed that both HDL and HbA1c were independent predictors of the before and after changes of total meiboscores (Table 6). Further investigation is essential to understand this multifactorial disease.

The strength of our study is that it is a pilot study on MG morphology among patients with dyslipidemia. To our knowledge it is the first prospective study on the possible relationship between oral HMG-CoA reductase inhibitors

and MGD. It is one of the few longitudinal studies on MG morphology using meibography.[20,28] One of the difficulties of a longitudinal meibography study is repositioning of the probe in the exact location at different times. In elderly patients, it was sometimes difficult to evert their tense eyelids to obtain optimal meibography images. Our study had limitations in that we had a relatively small sample size and a limited duration of follow-up. Second, statin treatment or control of lipid level might be beneficial only in the early stage of stagnant meibum without any obstruction. The beginning of lipid control might not be early enough in our study. In this stage, more advanced or invasive treatment, such as MG probing, might be required for possible salvation of glandular obstruction.[20] Third, our participants were mostly elderly patients which made it hard to differentiate the effect of aging and lipid. Fourth, more potential confounders need to be measured in future studies, as we had a heterogeneous group of participants. The initiation of lipid control was different in the time frame between the 2 groups. This problem could be addressed by a future longitudinal study involving a single group of participants over an extended period. Participants may be observed from early lifestyle interventions until they have statin treatment for a prolonged period. Other limitations of our study include unaddressed risk factors of MG disease, such as menopause or benign prostatic hyperplasia,[5] and behavorial measures, such as contact lens wearing.[60]

In conclusion, our study revealed that MGD progression occurred despite lipid control, as measured by meiboscores, meibum quality, and MG lid features. The underlying dry eye condition remained stationary throughout our study.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

KUAN-I. WU: METHODOLOGY, INVESTIGATION, DATA curation, Formal analysis, Visualization, Writing - original draft. **Chin-Ying Chen:** Investigation, Resources, Formal analysis, Writing - review & editing. **Tzuu-Shuh Jou:** Investigation, Resources, Formal analysis, Writing - review & editing. **Jyh-Ming Jimmy Juang:** Investigation, Resources, Formal analysis, Writing - review & editing. **Jin-Ying Lu:** Investigation, Resources, Formal analysis, Writing - review & editing. **I-Jong Wang:** Conceptualization, Methodology, Investigation, Resources, Validation, Writing - review & editing, Supervision, Project administration.

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