

Association of the severity of meibomian gland dysfunction with dyslipidemia in Indian population

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Purpose: To correlate the severity of meibomian gland dysfunction (MGD) with the serum lipoprotein levels. **Methods:** The study was conducted as a prospective observational study over a period of 18 months. Ninety patients diagnosed with MGD were enrolled after they gave their informed consent according to the inclusion–exclusion criteria. Meibomian gland status was evaluated by meibum quality, expressibility, and numerical scoring. Lipid profile was done from an overnight fasting blood sample and evaluated for total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TGs). **Results:** Patients with higher stages of MGD more often had serum TGs >150 mg/dL, total cholesterol >200 mg/dL, an LDL >130 mg/dL, and serum HDL >40 mg/dL, and there exists an association between increasing stage of MGD, and age, female sex, and increasing values of all the lipid profile components. **Conclusion:** A very strong association exists between increasing age and increasing severity of stage of MGD. A positive association exists between female sex and increasing severity of stage of MGD. A positive association exists between increasing severity of MGD and increasing levels of all the components of lipid profiles, namely LDL, HDL, total cholesterol, and triglycerides.

Key words: Dyslipidemia, meibomian gland disease, severity of dyslipidemia

Tim McAvoy once said: “Those little things can add up to make a big difference.” Similarly, the concept of meibomian gland dysfunction (MGD) may appear to be subordinate but may turn out to be one of the essential factors influencing the visual performance.

The term “Meibomian gland dysfunction” first appeared in the literature in 1980 and was used interchangeably with other eyelid conditions such as posterior blepharitis, meibomitis, meibomianitis, and meibomian keratoconjunctivitis,^[1] at least till 2011. MGD is one of the most underrecognized, underappreciated, and undertreated disease in ophthalmic practice. MGD is a chronic diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.^[2] Patients may present with dry eye, redness, irritation, itching, burning sensation, unstable fluctuating vision, and occasionally blurred vision with visual tasks. Recent studies showed that the prevalence of MGD in general population varies between 30.5 and 54.1%.^[3,4]

MGD is classified into low delivery forms (hyposecretory and obstructive) and high delivery forms (hypersecretory/seborrheic). Obstructive MGD is thought to be the most common variety.^[5] Both hyposecretory and hypersecretory MGD are influenced by endogenous factors, such as age, sex, hormonal disturbances, as well as by exogenous factors such as topical medications.^[2] The

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Manuscript received: 01.01.18; **Revision accepted:** 13.06.18

Access this article online

Website:

www.ijo.in

DOI:

10.4103/ijo.IJO_1256_17

Quick Response Code:



obstructive process, however, causes stagnation of meibum in the ductules, which can then undergo mechanical and chemical changes. Studies have shown that meibomian gland secretion in patients with MGD has an increased melting point and hence altered viscosity.^[6]

As meibomian gland secretion is lipid in nature, it is only logical to search for a possible link between systemic lipid level abnormalities and meibomian lipids. The primary purpose of this study was to determine if there was an association between dyslipidemia and MGD. The secondary purpose of this study was to identify the factors, if any, that play a role in this association.

Methods

The study was conducted as a prospective observational over a period of 18 months. Ethical approval was obtained from the Institutional Ethics Committee (IRB). Ninety consecutive patients diagnosed with MGD and 90 age and sex-matched controls were enrolled after they gave their informed consent. The only two inclusion criteria were patients aged 18–54 years, and those diagnosed with MGD based on the signs and symptoms. Patients with age <18 and >54 years were excluded. Exclusion criteria included patients with infectious keratoconjunctivitis or inflammatory ocular surface disorder

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Cite this article as: Guliani BP, Bhalla A, Naik MP. Association of the severity of meibomian gland dysfunction with dyslipidemia in Indian population. Indian J Ophthalmol 2018;66:1411-6.

unrelated to MGD; recent ocular surgery, alterations of lacrimal drainage system; concomitant topical medications especially for glaucoma; topical ophthalmic steroids taken during 4 weeks before the study; treatment with drugs affecting tearing (antihypertensives/cholinergics/OCPs/isotretinoin); pregnancy; presence of Sjogren syndrome, Rosacea, Parkinson's disease, and patients with cholestatic liver disease. This study was approved by the hospital ethical committee.

Once patients were selected, baseline assessment included:

- Symptoms scaled according to Ocular Surface Disease Index questionnaire^[7] (mild/moderate/severe)
- Measurement of blink rate and blink interval^[8] (average taken 12–15/min)
- Measurement of lower tear meniscus height.^[5,9] (cut-off: 1.5 mm)
- Assessment of tear film breakup time^[5,9] (cut-off: 10 seconds)
- Grading of corneal and conjunctival fluorescein staining: Oxford^[9] and DEWS scale
- Schirmer's test^[5,9] (cut-off: 10 cm)
- Lacrimal drainage system was assessed (presence of DCR scar, soft/hard blocks, ectropion/entropion).

Positive (abnormal) results in tests 1, 4, 5, and 6 provide partial evidence of the presence of a generic dry eye, without specifying whether it is aqueous-deficient or evaporative. Evidence of aqueous-deficient dry eye was obtained by measuring tear flow or an assessment of aqueous volume on the basis of tear meniscus height or Schirmer test.

- Meibomian gland status:

Assessed by the following indices:^[10]

a. Meibum quality:

It was assessed in each of eight glands of central third of the lower eyelid on a 0–3 scale for each gland:

0 = clear meibum

1 = cloudy meibum

2 = cloudy with debris

3 = thick like toothpaste (range 0–24)

b. Expressibility of meibum, which was assessed from 5 glands of central third of the lower eyelid on a scale of 1 to 3.

1 = 3–4 glands expressible

2 = 1–2 glands expressible

3 = no glands expressible

c. Numerical staining

Scores refer to a summed score of staining of the exposed cornea and conjunctiva. Fluorescein and Rose Bengal stains were used. The Oxford scale has a range of 0–15 and the DEWS scale has a range of 0–33.

This grading was obtained by firm digital pressure over the central third of upper and lower eyelid, while observing the ease of excretion and quality of meibum under a slit lamp biomicroscope.

Clinical staging of MGD

According to the report submitted by the International Workshop on Meibomian Gland Dysfunction and Management in 2011, MGD is divided into four stages, taking both the symptoms and clinical signs into consideration.

Stage 1: No symptoms of ocular discomfort, itching, or photophobia. Clinical signs based on gland expression are:

- Minimally altered secretions: Greater than or equal to grade 2 to less than grade 4
- Expressibility: 1.

No ocular surface staining present.

Stage 2: Minimal to mild symptoms of ocular discomfort, itching, or photophobia.

Minimal to mild MGD clinical signs

- Scattered lid margin features
- Mildly altered secretions: Greater than or equal to grade 4 to less than grade 8
- Expressibility: 1.

None to limited ocular surface staining (DEWS grade 0–7; Oxford grade 0–3).

Stage 3: Moderate symptoms of ocular discomfort, itching, or photophobia with limitations of activities.

Moderate MGD clinical signs

- Increased lid margin features: plugging, vascularity
- Moderate altered secretions: Greater than or equal to grade 8 to less than grade 13
- Expressibility: 2.

Mild-to-moderate conjunctival and peripheral corneal staining, often inferior (DEWS grade 8–23; Oxford grade 4–10).

Stage 4: Marked symptoms of ocular discomfort, itching, or photophobia with definite limitations of activities

Severe MGD clinical signs

- Increased lid margin features: dropout, displacement
- Severely altered secretions: Grade ≥ 13
- Expressibility: 3.

Increased conjunctival and corneal staining, including central staining (DEWS grade 24–33; Oxford grade 11–15).

Lipid profile: Done after overnight fasting. 2 mL blood was drawn in plain vial. Lipid profile was done on fully automated clinical chemistry analyzer Hitachi 912 using commercially available kits for the same at Department of Clinical Biochemistry.

- Parameters measured were:

- Triglycerides (TG): Hypertriglyceridemia >150 mg/dL
- Total cholesterol (TC): Hypercholesterolemia >200 mg/dL
- Low-density lipoprotein (LDL) cholesterol (LDL-C): High LDL >130 mg/dL
- High-density lipoprotein (HDL) cholesterol (HDL-C): High HDL >40 mg/dL.

Statistical analysis

This involved the detection of hyperlipidemia in patients found to have MGD. Statistical evaluation was done by calculating the prevalence of dyslipidemia in patients with MGD as compared to age and sex-matched controls. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean \pm SD and median. Qualitative variables were correlated using Chi-square test/Fisher's exact test. Spearman's correlation coefficient was used to assess the correlation between age and stage. A *P* value of <0.05 was considered statistically significant. The data were entered in MS Excel spreadsheet and analysis was done using Statistical Package for the Social Sciences (SPSS) version 21.0.

Results

Age-wise distribution of study subjects

The number of patients in the age groups <30, 31–40, 41–50, >50 were 28 (31.11%), 25 (27.78%), 24 (26.67%), and 13 (14.44%), respectively [Table 1]. Fig. 1 represents the age-wise distribution of patients as compared to the stage of MGD. Maximum number of patients belonged to stage 2, whereas stage 4 had the least number of patients. Similarly, maximum number of patients in our study were <30 years of age, while lesser patients belonged to the >50 age group. Because the *P* value = 0.00002, it indicates a very strong association between increasing age with respect to increasing severity of stage of MGD.

The scatter diagram in Fig. 2 represents the strength of the correlation between increasing age with respect to increasing severity of MGD. The Spearman’s correlation coefficient is 0.582 (0.426–0.704), indicative of a fairly strong positive correlation (at *P* < 0.0001) between age and severity of MGD.

Sex ratio

Out of the 90 patients enrolled in the study, 41 (45.56%) were male while female comprised 49 (54.44%) [Table 2]. As seen in Fig. 3, maximum number of patients belonged to stage 2, whereas stage 4 had the least number of patients. However, maximum number of female patients in our study belonged to stage 3, while maximum number of male patients belonged to stage 2.

Because the *P* value = 0.023, it indicates a very strong association between females and increasing severity of stage of MGD.

Total cholesterol and MGD

The number of MGD patients with TC <200 mg/dL and >200 mg/dL were 67 (74.44%) and 23 (25.56%), respectively. As seen in Fig. 4, even though maximum number of patients belonged to stage 2, whereas stage 4 had the least number of patients. Maximum number of patients with TC <200 mg/dL in our study belonged to stage 2, while maximum number of patients with TC >200 mg/dL belonged to stage 3. Because the

P value <0.0001, it indicates a very strong association between hypercholesterolemia (levels >200 mg/dL) and increasing severity of stage of MGD.

LDL and MGD

The number of MGD patients with LDL <130 mg/dL and >130 mg/dL were 65 (72.22%) and 25 (27.78%), respectively. Fig. 5 shows that although maximum number of patients belonged to stage 2, whereas stage 4 had the least number of patients, yet the maximum number of patients with LDL cholesterol <130 mg/dL in our study belonged to Stage 2, while maximum number of patients with LDL cholesterol >130 mg/dL belonged to stage 3. Because the *P* value <0.0001, it indicates a very strong association between increased LDL (levels >130 mg/dL) and increasing severity of stage of MGD.

HDL and MGD

The number of patients with HDL <40 mg/dL and >40 mg/dL were 50 (55.56%) and 40 (44.44%), respectively. Fig. 6 shows that maximum number of patients with HDL cholesterol <40 mg/dL in our study belonged to stage 2, while maximum number of patients with HDL cholesterol >40 mg/dL belonged to stage 3. Because the *P* value is 0.012 (<0.0001), it indicates a very strong association between decreased HDL (levels <40 mg/dL) and increasing severity of stage of MGD.

TGs and MGD

The number of patients with TGs <150 mg/dL and >150 mg/dL were 53 (58.89%) and 37 (41.11%), respectively. In Fig. 7, maximum number of patients belonged to stage 2, whereas stage 4 had the least number of patients. However, maximum number of patients with TGs <150 mg/dL in our study belonged to stage 2, while maximum number of patients with TGs >150 mg/dL belonged to stage 3. Because the *P* value is 0.006 (<0.0001), it indicates a very strong association between increased TGs (levels <150 mg/dL) and increasing severity of stage of MGD.

Table 1: Age-wise demographic characteristics of patient data

	Stage of MGD				Total	P
	1	2	3	4		
Age						
<OR=30	8 (61.54%)	19 (45.24%)	1 (3.85%)	0 (0.00%)	28 (31.11%)	0.00002
31-40	3 (23.08%)	15 (35.71%)	4 (15.38%)	3 (33.33%)	25 (27.78%)	
41-50	2 (15.38%)	5 (11.90%)	14 (53.85%)	3 (33.33%)	24 (26.67%)	
>50	0 (0.00%)	3 (7.14%)	7 (26.92%)	3 (33.33%)	13 (14.44%)	
Total	13 (100%)	42 (100%)	26 (100%)	9 (100%)	90 (100%)	

Table 2: Sex-wise demographic characteristics of patient data

	Stage of MGD				Total	P
	1	2	3	4		
Sex						
Female	6 (46.15%)	17 (40.48%)	20 (76.92%)	6 (66.67%)	49 (54.44%)	0.023
Male	7 (53.85%)	25 (59.52%)	6 (23.08%)	3 (33.33%)	41 (45.56%)	
Total	13 (100%)	42 (100%)	26 (100%)	9 (100%)	90 (100%)	

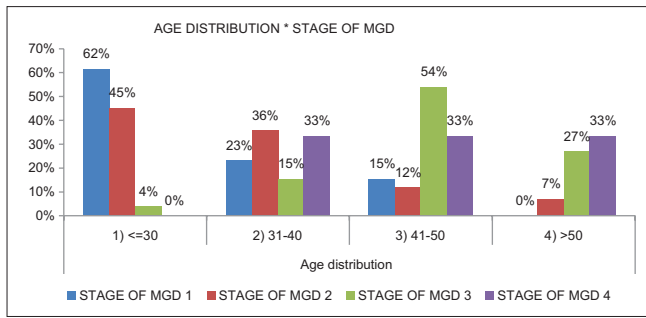


Figure 1: Age-wise distribution with respect to stage of MGD

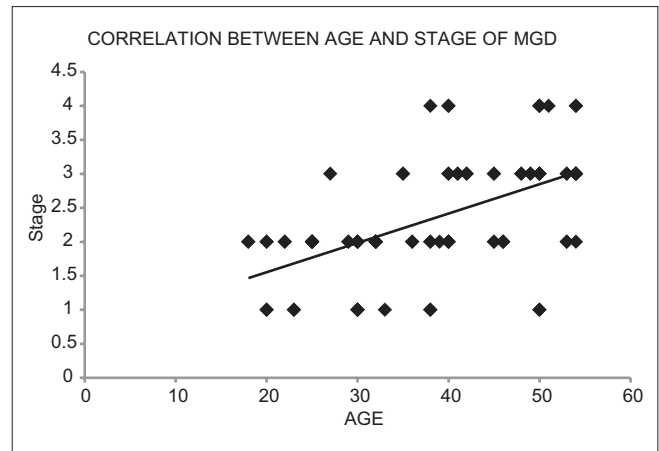


Figure 2: Scatter diagram for age of patient and stage of MGD

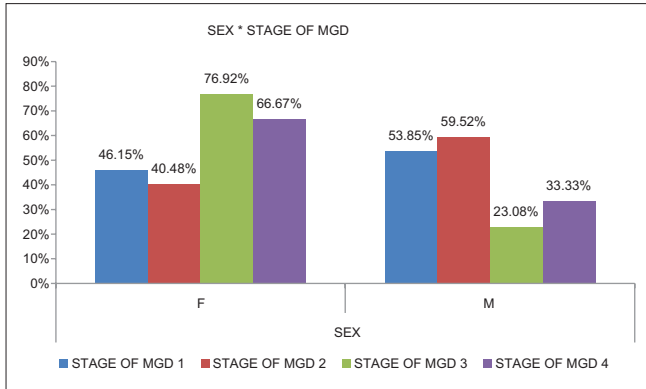


Figure 3: Sex of patients and stage of MGD

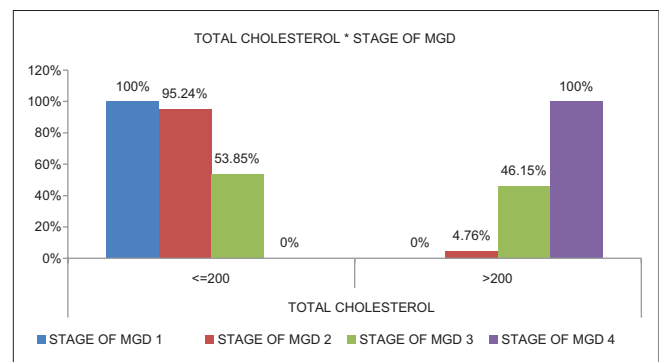


Figure 4: Total cholesterol and stage of MGD

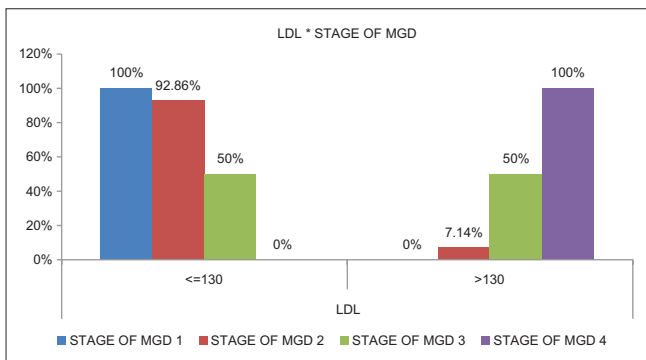


Figure 5: LDL and stage of MGD

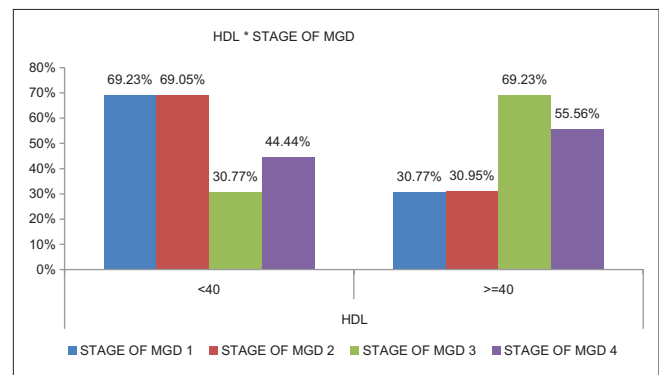


Figure 6: HDL and stage of MGD

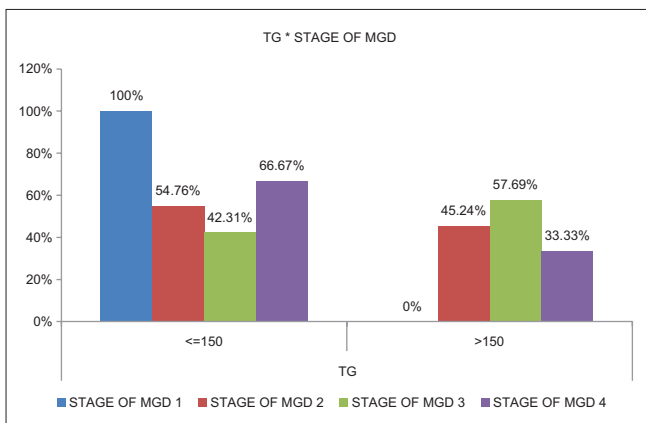


Figure 7: TGs and stage of MGD

Controls

The number of age and sex-matched controls with TC <200 mg/dL and >200 mg/dL were 76 (84.44%) and 14 (15.56%), respectively. The number of age and sex-matched controls with LDL <130 mg/dL and >130 mg/dL were 74 (82.22%) and 16 (17.78%), respectively. The number of age and sex-matched controls with HDL <40 mg/dL and >40 mg/dL were 46 (51.11%) and 44 (48.88%), respectively. The number of age and sex-matched controls with TGs <150 mg/dL and >150 mg/dL were 47 (52.23%) and 43 (47.77%), respectively.

Discussion

MGD can cause chronic ocular irritation and is seldom reported accurately. Some studies postulate an MGD prevalence of up to 70%.^[11,12] In clinical practice, however, mild asymptomatic cases may not be diagnosed. The cause of MGD is incompletely understood, but changes in meibum composition and/or obstruction of the meibomian glands is thought to be central to the process.^[13,14] Studies show that meibum of MGD patients has different components and proportions of cholesterol compared to the meibum of controls.^[15] Specifically, cholesterol esters were always present in the glands of patients with MGD but not necessarily in normal controls.^[16] Recent research postulates that increased cholesterol in meibum may play a role in the pathology of MGD.^[17] Cholesterol esters may even be a consequence of the dysfunction rather than its cause.

Organic substances with a greater number of saturated bonds or larger side chains have higher melting points.^[18] This concept can explain why the melting point of normal meibomian secretions ranges from 30 to 34°C, while cholesterol, with its numerous structural differences, has a typical melting point of 148°C.^[13] Theoretically, meibum with higher concentrations of cholesterol would be more viscous at physiological temperatures, thus clogging the meibomian glands. The tear film's lipid layer may get altered as a result of this obstruction, increasing tear evaporation, and in turn leading to evaporative dry eye disease. Many studies have been done in the past to find association between MGD and a deranged lipid profile.

Dyslipidemia is a term that represents an abnormal value in one or more of the lipid profiles. Certain types of dyslipidemia, i.e., low levels of HDL, high levels of LDL, and high levels of TC, have been shown to be independent risk factors for vascular pathological events.

In our study, we found a strong association between increasing age and severity of MGD. This is in accordance with a study by Villani *et al.*,^[19] which evaluated age-related changes of the meibomian gland using *in vivo* laser scanning confocal microscopy. Their work demonstrated that meibomian gland density and diameter significantly decreased with age. This observation is also consistent with the results obtained by Bukhari *et al.*,^[20] and Punit Briach *et al.*^[21] study.

The prevalence of dyslipidemia in the general population is well described by current literature,^[20] which extrapolated data from the National Health and Nutrition Examination Survey. The prevalence of TC >200 mg/dL is 45.1% and TC >240 mg/dL is 15.7%. The prevalence of LDL >130 mg/dL is 32.8%, HDL <40 mg/dL is 15.5%, and TGs >150 mg/dL is 33.1%.^[22]

The number of MGD patients with TC <200 mg/dL and >200 mg/dL in our study were 67 (74.44%) and 23 (25.56%), respectively. Maximum number of patients with TC <200 mg/dL belonged to stage 2, while maximum number of patients with TC >200 mg/dL belonged to stage 3. As the *P* value is <0.0001, it indicates a strong association between hypercholesterolemia (levels >200 mg/dL) and increasing severity of stage of MGD. This is consistent with the findings obtained in the studies conducted by Dao *et al.*^[23] and Bukhari *et al.*^[20]

The number of MGD patients with LDL cholesterol <130 mg/dL and >130 mg/dL were 65 (72.22%) and 25 (27.78%), respectively. Maximum number of patients belonged to stage 2, whereas stage 4 had the least number of patients. Maximum number of patients with LDL cholesterol <130 mg/dL in our study belonged to stage 2, while maximum number of patients with LDL cholesterol >130 mg/dL belonged to stage 3. Because the *P* value is <0.0001, it indicates a strong association between increased LDL (levels >130 mg/dL) and increasing severity of stage of MGD. This observation is also consistent with the findings of all the previous mentioned studies.^[19-25]

Maximum number of patients in our study belonged to stage 2, whereas stage 4 had the least number of patients. However, maximum number of patients with HDL cholesterol <40 mg/dL in our study belonged to stage 2, while maximum number of patients with HDL cholesterol >40 mg/dL belonged to stage 3. As the *P* value is 0.012 (<0.012), it indicates a fairly strong association between increased HDL (levels <40 mg/dL) and increasing severity of stage of MGD. This observation is in accordance with the study conducted by Dao *et al.* in 2009, and by Pinna *et al.* in 2013. Their study was concluded with the observation that the component which contributed most to hypercholesterolemia found in moderate-to-severe MGD patients was increased HDL levels. This presents as a surprise, as elevated HDL has not yet been associated with any pathological state. Abnormal systemic lipid processing maybe the unrecognized cause of elevated HDL levels in such patients. However, all other similar studies found no association between increased HDL levels and increasing severity of MGD, and reported increased LDL levels to be responsible for the increasing severity of MGD. In our study even increasing LDL levels have been significantly found to be associated with the increasing severity of MGD.

TG levels were found to be significantly associated with increasing severity of MGD, in our study. All the other studies found increased TGs in moderate and severe MGD cases, but could not reach statistical significance. Meibomian gland secretions contain TGs in addition to cholesterol, which is known to constitute 1–2% of the normal meibomian glands secretions, and the increase in serum TGs might have a role in increasing the meibum melting point and increasing its viscosity.

Our study has found out that patients with higher stages of MGD more often had serum TGs >150 mg/dL, TC >200 mg/dL, an LDL >130 mg/dL, and serum HDL >40 mg/dL, and there exists an association between increasing stage of MGD, and age, female sex, and increasing values of all the lipid profile components [Table 3]. However, a prospective observational study, as ours, cannot establish a “cause and effect” relationship. A larger prospective study is required to show that abnormal serum cholesterol levels can cause MGD. Secondly, the etiology of MGD is unknown and may be multifactorial. Thirdly, the sample size was small, obviating the need for larger studies to further strengthen this observation. Fourthly, all the participants in our study were Indians, limiting the generalizability of this study. MGD may be a possible marker of yet undiagnosed hypercholesterolemia, regardless the type of cholesterol involved, either “bad” or “good.” Moreover, if a causal relationship between dyslipidemia and MGD is proved by prospective studies, oral lipid-lowering medications may be

Table 3: Summary of patients of MGD with respect to their lipid profiles

	Sample size	Mean±SD	Median	Min–Max	Interquartile range
Age in years	90	38.33±10.87	39.5	18-54	30-49
HDL in mg/dL	90	42.56±20.76	38	20-155	30-46
LDL in mg/dL	90	116.41±50.15	104.5	38-283	84-151
TG in mg/dL	90	149.78±63.01	132.5	63-289	99-208
TC in mg/dL	90	186.44±59.11	176	99-352	141-203

tried by clinicians for the treatment of MGD. Further studies are needed to evaluate the effect of controlling serum triglyceride and LDL levels on controlling MGD.

Conclusion

A very strong association exists between increasing age and increasing severity of stage of MGD. A positive association exists between female sex and increasing severity of stage of MGD. A positive association exists between increasing severity of MGD and increasing levels of all the components of lipid profile namely LDL, HDL, Total cholesterol and Triglycerides.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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