*Original Article*

# Association of Lipid Profile with Severity of Meibomian Gland Dysfunction

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## Abstract

**Introduction:** The impact of Meibomian gland dysfunction (MGD) on the overall health of the patient is not known. Efforts are being made to understand the association of dyslipidemia with MGD. The objective of the study was to determine the association of dyslipidemia with the severity of MGD, a contributor to dry eye syndrome.

**Materials and methods:** We performed an observational case-control study at a tertiary care centre over 18 months and enrolled 116 patients in the age group of 18 to 65 years. A detailed history and clinical examination were done. Following examination, patients were allocated into two groups, patients with MGD and no history of dyslipidemia (cases) and patients without MGD and no history of dyslipidemia (controls). A fasting lipid profile was done for both these groups. The data were subsequently analyzed with SPSS software.

**Results:** 56 (48.3%) of the participants had serum total cholesterol levels ≥200 mg/dl, with a significant association between higher cholesterol levels and severity of MGD (p=0.0001). 77 (66.4%) of the participants had serum triglycerides levels of ≥150 mg/dl. There was a significant association between the severity of MGD and elevated triglyceride levels (95% confidence interval of Pearson's chi-square 28.16, p=0.0001). A significant association was also observed between the severity of MGD and elevated LDL levels (95% confidence interval of Pearson's chi-square 5.95, p=0.015). However, no association was found between HDL levels and the severity of MGD.

**Conclusion:** The results suggest that patients with MGD and without any history of dyslipidemia, may have higher blood levels of lipid profile components as compared to age-matched controls.

**Key words:** Lipid profile, Meibomian gland dysfunction, Dry eye.

## Introduction

Meibomian gland dysfunction (MGD) is a meibomian gland abnormality, in which there is duct obstruction along with abnormal glandular secretions. This may lead to tear film changes, inflammation, and disease of the ocular surface. Classification of MGD includes two major categories. Low delivery states because of decreased glandular secretion or

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duct obstruction and high delivery states due to excessive secretion. Patients may present with symptoms of ocular discomfort while performing various visual tasks. The prevalence of MGD is known to be much higher in Asian populations. It has been reported to be over 60% in various studies (Nichols et al., 2011).

Owing to the lipid nature of meibomian gland secretions, dyslipidemia may be associated with MGD. Recent studies have reported that patients with MGD may have higher total blood cholesterol levels as compared to the general population (Dao et al., 2010 and Bukhari et al., 2013). Epidemiological studies have firmly established abnormal lipids as significant risk factors for cardiovascular disease and stroke (Shi et al., 2016).

The impact of MGD on the overall health of the patient is often overlooked. Ophthalmologists may be the first to detect systemic diseases such as cardiovascular disease, due to their ocular manifestations like amaurosis fugax. Similarly, the presence of MGD may point towards an unrecognized underlying systemic disorder.

## Material and methods

The study was conducted as an observational case-control study over one and a half years after obtaining ethical approval from the Ethics Committee of the Institute. The estimated sample size (n = 116) was calculated based on the odds ratio of 3.5, confidence interval of 95% and the ratio of control: cases=1:1. Fifty eight patients diagnosed with MGD and no history of dyslipidemia (cases) and 58 age and sex-matched patients without MGD and no history of dyslipidemia (controls) were enrolled after their written, informed consent. Exclusion criteria for all patients were age less than 18 and more than 65 years, infectious keratoconjunctivitis, ocular surface disorders not related to MGD, ocular surgery in last six months, topical anti-glaucoma medications and topical ophthalmic steroids instilled during four weeks before commencement of the study, treatment with drugs affecting lacrimation, presence of Sjögren syndrome, Acne rosacea and patients with cholestatic liver disease and pregnancy. Patients with a history of intake of anti-lipid drugs were also excluded from the study.

Patients were diagnosed with MGD by clinical examination based on glandular obstruction and quality of meibum. Meibomian gland status was assessed by the following indices

1. Meibum quality: It was assessed from eight glands of the central one-third of the lower eyelid on a 0–3 scale for each gland:
   0= clear meibum
   1= cloudy meibum
   2= cloudy meibum with debris
   3= thick toothpaste-like meibum
2. Expressibility of meibum was assessed from five glands of the central one-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
3. Numerical staining scores were the summation of staining scores(Fluorescein and Rose Bengal stains) of the exposed cornea and conjunctiva.

Serum lipid profile was measured after overnight fasting. Dyslipidemia was defined as Total Cholesterol >200 mg/dL, Triglycerides >150 mg/dL, Low-density lipoproteins (LDL) >130 mg/dL and High-density lipoproteins (HDL) <40 mg/dL.

## Statistical analysis

The prevalence of dyslipidemia in patients with MGD as compared to age and gender-matched controls was calculated. The Chi-square test/ Fischer's exact test was used for qualitative variables. Spearman's coefficient was used to assess the correlation between the stage of MGD and age. Significance levels were kept at $p < 0.05$. Statistical Package for the Social Sciences (SPSS) version 21.0 software was used for data analysis.

## Results

A total of 116 patients were included with a mean age of 48.86 years (SD 12.11 years, range 20–65 years). There were 58 cases and an equal number of age and gender-matched controls. Mean age of the cases and controls was 49 years .There were 60 males (30 cases and 30 controls) and 56 females (28 cases and 28 controls). Figure 1 and Table 1 show the distribution of patients according to their age and stages of MGD. A significant difference was observed between the five groups in terms of age and stage of MGD, with the median age (Years) being highest in the MGD: Grade 4 group. Because the P value=0.002, it indicates that the severity of MGD was more in the older age group. Figure 2 and Table 2 represent the gender distribution of patients with various stages of MGD. No significant association was seen between gender and severity of MGD (p =0.841). Figure 3 and Table 3 represent the distribution of the stage of MGD and its association with dyslipidemia. 50.0% (58/116) of participants had no evidence of MGD, 9.5%(11/116) had grade 1 MGD, 27.6%(32/116) had grade 2 MGD, 10.3% (12/116) had grade 3 MGD and 2.6% (3/116) of the participants had grade 4 MGD. As the p-value is less than 0.001, it indicates the presence of a strong association of severity of MGD with dyslipidemia.

56 (48.3%) of the participants had serum total cholesterol levels ≥200 mg/dl. The study showed a significant association between higher cholesterol levels and MGD severity (p=0.0001) (Table 4 and figure 4). 77 (66.4%) of the participants had serum triglycerides levels of ≥150 mg/dl. There was a significant association between the severity of MGD and elevated triglyceride levels with a 95% confidence interval of Pearson's chi-square to be 28.16, p=0.0001 (Table 5 and figure 5). 7 (6%) of the participants had serum HDL levels <40 mg/dl. The study showed no association between the severity of MGD and low HDL levels with a 95% confidence interval, p=0.114 (Table 6 and figure 6). 12 (10.3%) of the participants had serum total triglycerides levels of ≥130 mg/dl. The study showed a significant association between the severity of MGD and elevated LDL levels with a 95% confidence interval of Pearson's chi-square 5.95, p=0.015 (Table 7 and figure 7). Table 8 shows that none of the lipid parameters (total cholesterol, triglycerides, HDL or LDL) have any significant relationship with the occurrence of Grade 1 MGD according to multivariate logistic regression analysis. With Grade 2 MGD, the analysis observed a statistically significant role of total cholesterol (p<0.001). With Grade 3 MGD, the role of both total cholesterol (p=0.001) and triglycerides (p=0.017) were found to be statistically significant, while with Grade 4 MGD, the analysis showed a statistically significant role of triglycerides only (p=0.023).

**Table 1: Comparison of the five groups in Terms of Age (Years) (n = 116)**

| Age (Years) | MGD | | | | | | |
|---|---|---|---|---|---|---|---|
| | Controls | Grade 1 | Grade 2 | Grade 3 | Grade 4 | F | p-value* |
| Mean (SD) | 48.81 (12.18) | 38.18 (11.06) | 49.34 (10.67) | 54.92 (11.94) | 59.67 (4.51) | 3.843 | 0.006 |
| Range | 21 - 64 | 22 - 49 | 21 - 65 | 20 - 64 | 55 – 64 | | |

* One-way ANOVA: Post-hoc Bonferroni test showed p=0.007 for pairwise comparison of groups 1 and 3 (significant) and p>0.05 for other pairwise comparisons

**Table 2: Association Between grades of MGD and Gender (n = 116)**

| Gender | Controls | MGD | | | | Total | |
|---|---|---|---|---|---|---|---|
| | | Grade 1 | Grade 2 | Grade 3 | Grade 4 | | |
| Male | 30 (50.0%) | 7 (11.7%) | 16 (26.7%) | 5 (8.3%) | 2 (3.3%) | 60 (100.0%) | p=0.86* |
| Female | 28 (50.0%) | 4 (7.1%) | 16 (28.6%) | 7 (12.5%) | 1 (1.8%) | 56 (100.0%) | |
| Total | 58 (50.0%) | 11 (9.5%) | 32 (27.6%) | 12 (10.3%) | 3 (2.6%) | 116 (100.0%) | |

* Fischer's Exact Test

**Table 3: Association Between MGD and Dyslipidemia (n = 116)**

| Dyslipidemia | Controls | MGD | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | | Cases | Grade 1 | Grade 2 | Grade 3 | Grade 4 | | |
| Present | 29 (34.5%) | 55 (65.5%) | 9 (10.7%) | 31 (36.9%) | 12 (14.3%) | 3 (3.6%) | 84 (100.0%) | p<0.0001* |
| Absent | 29 (90.6%) | 3 (9.4%) | 2 (6.2%) | 1 (3.1%) | 0 (0.0%) | 0 (0.0%) | 32 (100.0%) | Odds Ratio = 18.33 |
| Total | 58 (50.0%) | 58 (50.0%) | 11 (9.5%) | 32 (27.6%) | 12 (10.3%) | 3 (2.6%) | 116 (100.0%) | |

* X^2 = 29.17, df=1

**Table 4: Association Between MGD and Total Cholesterol (n = 116)**

| Total Cholesterol | Controls | MGD | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | | Cases | Grade 1 | Grade 2 | Grade 3 | Grade 4 | | |
| <200 mg/dl | 47 (78.3%) | 13 (21 %) | 7 (11.7%) | 6 (10.0%) | 0 (0.0%) | 0 (0.0%) | 60 (100.0%) | p<0.0001* |
| ≥200 mg/dl | 11 (19.6%) | 45 (80.4%) | 4 (7.1%) | 26 (46.4%) | 12 (21.4%) | 3 (5.4%) | 56 (100.0%) | Odds Ratio = 0.0676 |
| Total | 58 (50.0%) | 58 (50 %) | 11 (9.5%) | 32 (27.6%) | 12 (10.3%) | 3 (2.6%) | 116 (100.0%) | |

* X^2 = 39.91, df=1

**Table 5: Association between MGD and Serum Triglycerides (n = 116)**

| Serum Triglycerides | | MGD | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Controls | Cases | Grade 1 | Grade 2 | Grade 3 | Grade 4 | | |
| <150 mg/dl | 33 (84.6%) | 6 (15.4%) | 3 (7.7%) | 3 (7.7%) | 0 (0.0%) | 0 (0.0%) | 39 (100.0%) | p <0.0001* |
| ≥150 mg/dl | 25 (32.5%) | 52 (67.5%) | 8 (10.4%) | 29 (37.7%) | 12 (15.6%) | 3 (3.9%) | 77 (100.0%) | Odds Ratio = 0.087 |
| Total | 58 (50.0%) | 58 (50.0%) | 11 (9.5%) | 32 (27.6%) | 12 (10.3%) | 3 (2.6%) | 116 (100%) | |

* X^2 = 28.16, df=1

**Table 6: Association between MGD and Serum HDL (n = 116)**

| Serum HDL | | MGD | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Controls | Cases | Grade 1 | Grade 2 | Grade 3 | Grade 4 | | |
| <40 mg/dl | 1 (14.3%) | 6 (85.7%) | 1 (14.3%) | 2 (28.6%) | 2 (28.6%) | 1 (14.3%) | 7 (100.0%) | p=0.112 * |
| ≥40 mg/dl | 57 (52.3%) | 52 (47.7%) | 10 (9.2%) | 30 (27.5%) | 10 (9.2%) | 2 (1.8%) | 109 (100.0%) | Odds Ratio = 6.58 |
| Total | 58 (50.0%) | 58 (50.0%) | 11 (9.5%) | 32 (27.6%) | 12 (10.3%) | 3 (2.6%) | 116 (100.0%) | |

* Fischer's Exact Test

**Table 7: Association between MGD and Serum LDL (n = 116)**

| Serum LDL | Controls | MGD | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | | Cases | Grade 1 | Grade 2 | Grade 3 | Grade 4 | | |
| <130 mg/dl | 56 (53.8%) | 48 (46.2%) | 10 (9.6%) | 27 (26.0%) | 10 (9.6%) | 1 (1.0%) | 104 (100.0%) | p=0.015 * |
| ≥130 mg/dl | 2 (16.7%) | 10 (83.3%) | 1 (8.3%) | 5 (41.7%) | 2 (16.7%) | 2 (16.7%) | 12 (100.0%) | Odds Ratio = 0.17 |
| Total | 58 (50.0%) | 58 (50.0%) | 11 (9.5%) | 32 (27.6%) | 12 (10.3%) | 3 (2.6%) | 116 (100.0%) | |

* X^2 = 5.95, df=1

**Table 8: Multivariate logistic regression analysis to quantify the effect of various lipid parameters on grade of MGD (n=116)***

| MGD Grade** | Intercept/ Covariates | B | Std. Error | Wald's Z | Significance level | Exp(B) | 95% Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower Bound | Upper Bound |
| 1 | Intercept | -5.192 | 3.593 | 2.088 | 0.148 | | | |
| | TC | 0.023 | 0.014 | 2.699 | 0.100 | 1.024 | 0.996 | 1.052 |
| | TG | 0.005 | 0.015 | 0.130 | 0.718 | 1.005 | 0.976 | 1.036 |
| | HDL | -0.011 | 0.024 | 0.189 | 0.664 | 0.990 | 0.944 | 1.038 |
| | LDL | -0.011 | 0.018 | 0.351 | 0.553 | 0.989 | 0.955 | 1.025 |
| 2 | Intercept | -10.795 | 3.363 | 10.306 | 0.001 | | | |
| | TC | 0.051 | 0.013 | 16.305 | <0.001 | 1.052 | 1.026 | 1.078 |
| | TG | 0.009 | 0.013 | 0.515 | 0.473 | 1.009 | 0.984 | 1.034 |
| | HDL | -0.017 | 0.022 | 0.606 | 0.436 | 0.983 | 0.942 | 1.026 |
| | LDL | -0.005 | 0.014 | 0.119 | 0.730 | 0.995 | 0.968 | 1.023 |
| 3 | Intercept | -34.110 | 8.718 | 15.308 | <0.001 | | | |
| | TC | 0.066 | 0.020 | 10.777 | 0.001 | 1.069 | 1.027 | 1.112 |
| | TG | 0.101 | 0.042 | 5.650 | 0.017 | 1.106 | 1.018 | 1.202 |
| | HDL | 0.001 | 0.038 | 0.001 | 0.975 | 1.001 | 0.930 | 1.078 |
| | LDL | -0.015 | 0.021 | 0.535 | 0.465 | 0.985 | 0.945 | 1.026 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 4 | Intercept | -46.363 | 16.286 | 8.104 | 0.004 | | | |
| | TC | 0.054 | 0.033 | 2.658 | 0.103 | 1.056 | 0.989 | 1.127 |
| | TG | 0.152 | 0.067 | 5.135 | 0.023 | 1.164 | 1.021 | 1.327 |
| | HDL | -0.047 | 0.086 | 0.303 | 0.582 | 0.954 | 0.807 | 1.128 |
| | LDL | 0.030 | 0.036 | 0.683 | 0.409 | 1.030 | 0.960 | 1.106 |

* Cox and Snell pseudo R-square = 0.626 ** Controls were considered as reference category

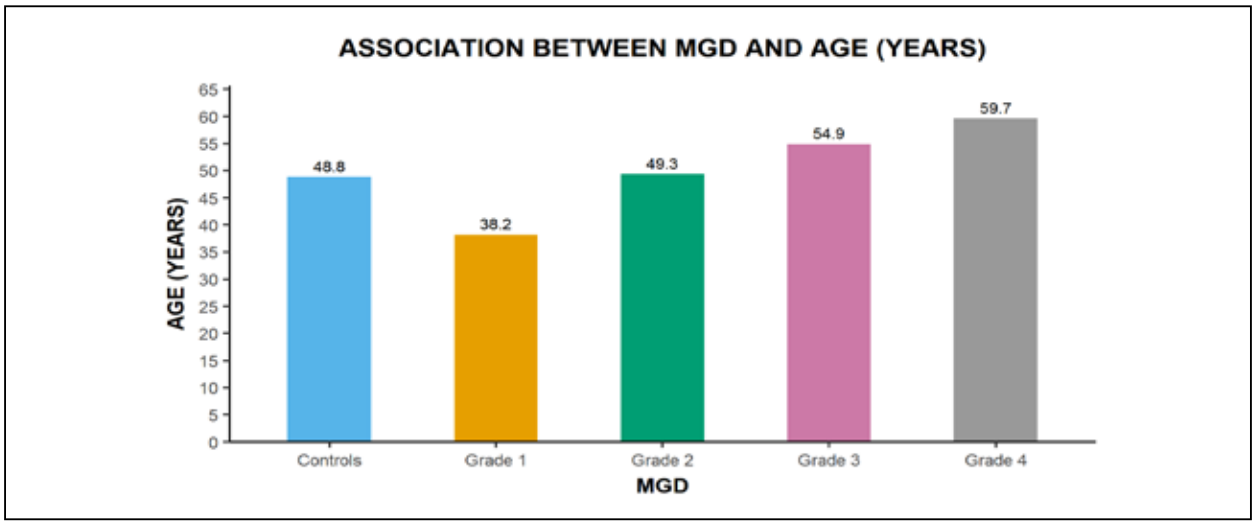


**Figure 1:** Bar graph showing the association between MGD and age in years (n=116)

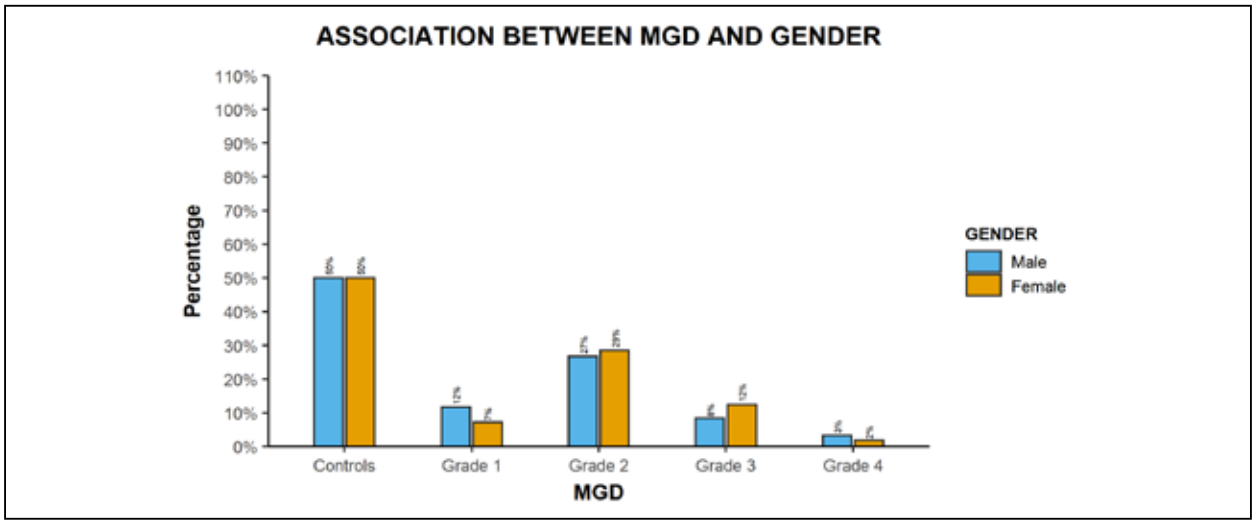


**Figure 2:** Bar graph showing the association between MGD and gender (n=116)

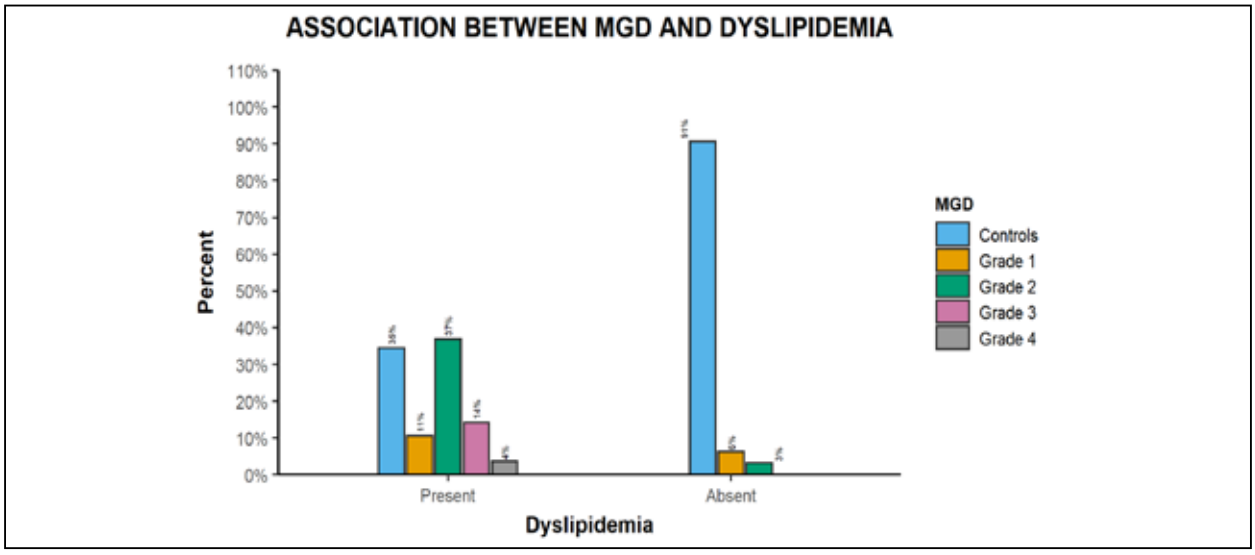


**Figure 3:** Bar graph showing the association between MGD and dyslipidemia (n=116)

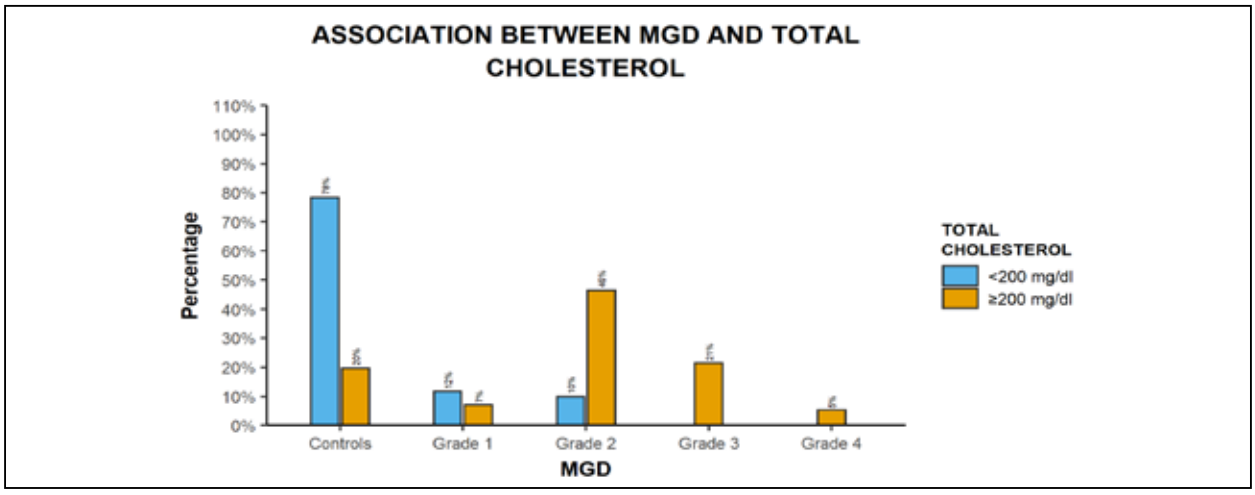


**Figure 4:** Bar graph showing the association between MGD and total cholesterol (n=116)

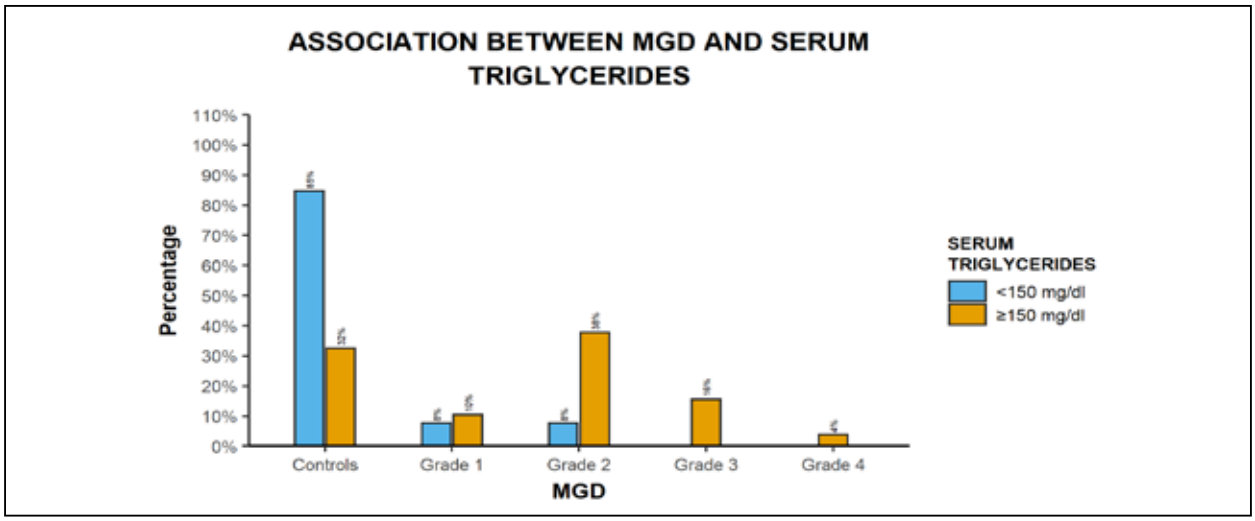


**Figure 5:** Bar graph showing the association between MGD and serum triglycerides (n=116)

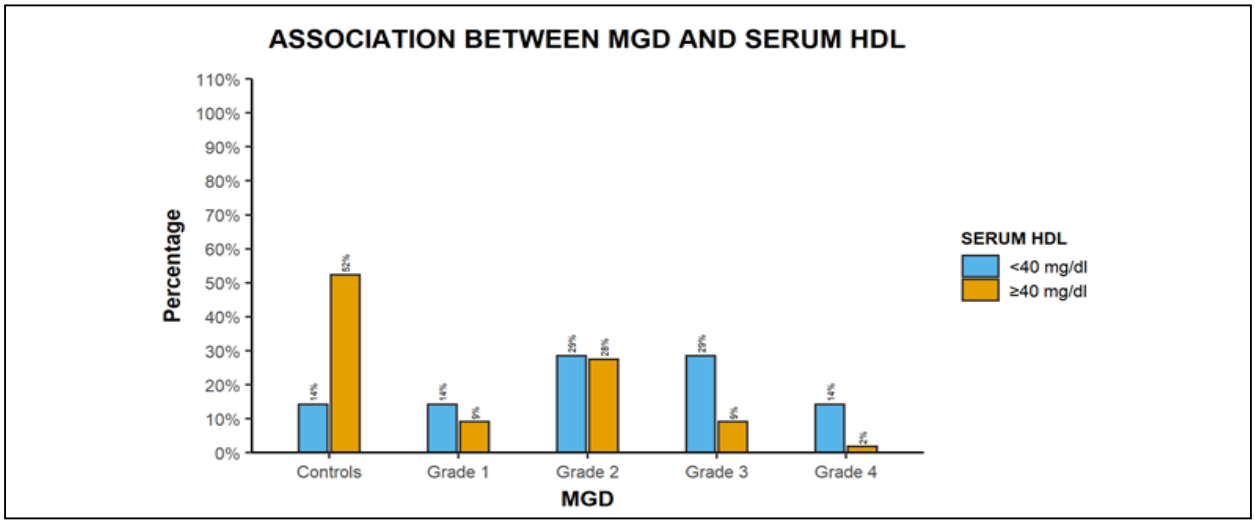


**Figure 6:** Bar graph showing the association between MGD and serum HDL (n=116)

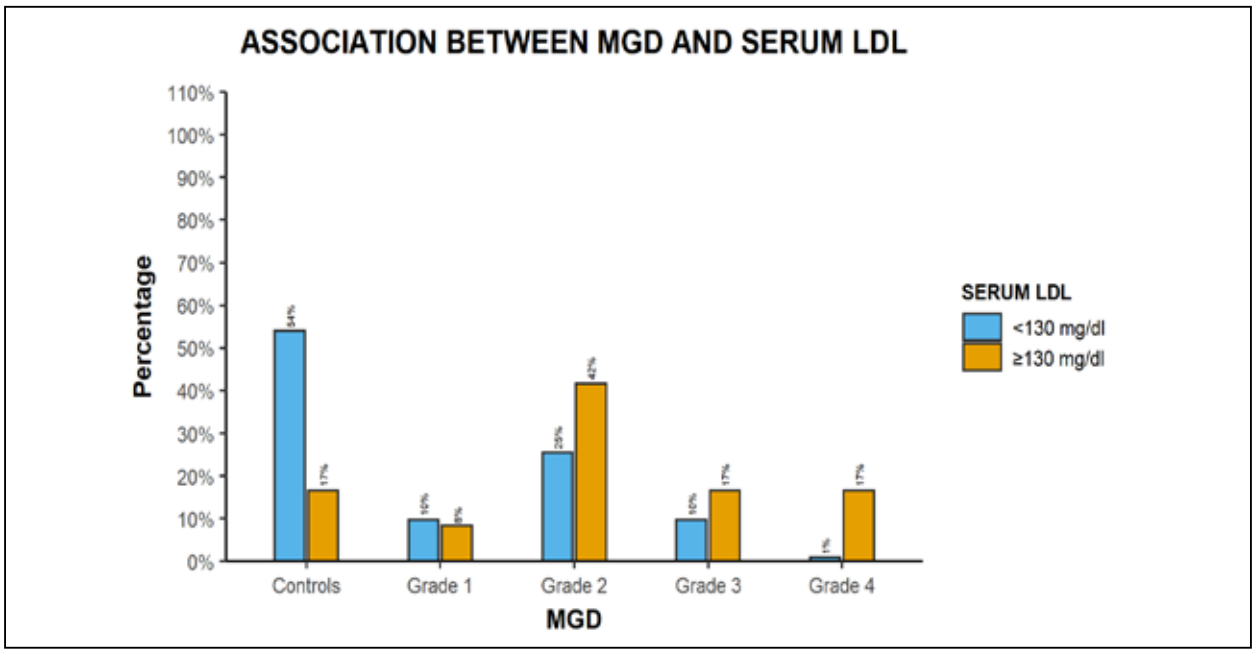


**Figure 7:** Bar graph showing the association between MGD and serum LDL (n=116)

## Discussion

Substances with heavier side chains or more saturation have higher melting points ( Chhadva et al., 2017). That explains why cholesterol has a melting point of 148 degrees Celsius as compared to 30 to 34 degrees Celsius for normal meibomian secretions (Butovich et al., 2010). Theoretically, meibum with higher cholesterol content should have a higher melting point and viscosity at body temperatures, leading to clogging of the meibomian glands. This may change the lipid layer of the tear film, causing more tear evaporation and higher tear osmolarity, leading to evaporative dry eye disease. The lipid of human meibum is similar in normal people, but may differ in persons with MGD (Green-Church et al., 2011). The obstructive process also depends on various

endogenous factors including age, sex, and hormonal disturbances, as well as exogenous factors such as the use of topical therapeutic agents(Shine et al., 1991).

Literature in the past suggested that higher systemic cholesterol levels may cause MGD. Hence, in our study we wanted to assess whether MGD was associated with higher cholesterol levels and other constituents of lipid profile namely LDL, HDL, and triglycerides (Dao et al., 2010; Pinna et al.,2013; Bukhari et al., 2013).

In our study, we found that increased patient age led to more severe MGD. This finding is similar to a study by Villani et al (Villani et al., 2013) and the results obtained by Bukhari et al*.,* 2013 and Briach et al., 2016.

Dao et al. conducted a retrospective case-control study, in which 66 patients over 18 months, with moderate to severe meibomian gland disease, were recruited and their serum lipid levels were obtained (Dao et al., 2010). According to this study, patients with MGD (moderate to severe) had a higher incidence of hypercholesterolemia and higher serum HDL cholesterol levels as compared to the normal population.

Bukhari et al. in 2013, studied 132 participants with MGD and 104 controls. They performed a correlation between serum fasting lipid levels and the severity of MGD (Bukhari et al., 2013). They found that MGD does not correlate with dyslipidemia.

Pinna et al. in 2013, conducted a pilot study on 60 symptomatic patients with MGD, and no history of hypercholesterolemia and 63 controls, over 18 months (Pinna et al.,2013). Hypercholesterolemia was found in 35 cases (58.3%) and 4 controls (6.3%),($p<0.0001$). According to this study, both LDL and HDL levels were increased in patients with MGD.

Jacob et al. in 2015, conducted a study on patients in the age group of 40-70 years in South India over 6 months (Jacob et al., 2015). Patients were allocated into two groups – patients with MGD (cases) and patients without MGD (controls). Significant correlation was found between total cholesterol levels and MGD (CI = 4.149 - 40.751; p= 0.01). This study also found a correlation between LDL and MGD (CI= 43.059 - 64.468; p= 0.0001). It was summarised that dyslipidemia is one of the major causes of MGD.

Braich et al. in 2015, enrolled109 patients with MGD and 115 controls (Braich et al., 2015). All participants were Indian, without any history of dyslipidemia. MGD was significantly associated with age, serum TG concentration ≥150 mg/dl, total cholesterol concentration ≥200 mg/dl and LDL concentration ≥130 mg/dl. They concluded that adults from rural, north India with MGD may have higher chances of dyslipidemia as compared to those without MGD.

Guliani et al in 2018, conducted a prospective observational study on 90 patients with MGD, over 18 months (Guliani et al.,2018). A positive association was found between increasing severity of MGD and dyslipidemia.

In our study, a very strong association was found to exist between increasing age and increasing severity of the stage of MGD. No association existed between gender and the increasing severity of the stage of MGD. There was a positive association between the severity of MGD and increasing levels of LDL, Total cholesterol and Triglycerides. However, no association was found between the severity of MGD and HDL levels. It appears that the onset of lower grade of MGD is related with serum total cholesterol levels, and as the severity of MGD increases, the role of triglycerides becomes important. Limitations of the study include small sample size, absence of objective tests like meibography and non-standardization of scoring systems for MGD.

## Conclusion

The results of the study suggests a strong positive association between increasing age and increasing severity of MGD. There is a positive association between the severity of MGD and components of the lipid profile, except for HDL. The Ophthalmologist should suspect dyslipidemia in MGD patients, which is a modifiable cardiovascular disease risk factor. Studies on larger populations are, however, needed to prove whether this association is indeed causal.

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