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Association of risk factors with severity of meibomian gland dysfunction

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ABSTRACT

BACKGROUND: Meibomian gland dysfunction (MGD) is an alteration in the function of meibomian glands, leading to decreased tear film stability. We aimed to assess the severity of MGD and correlate it with various risk factors.

MATERIAL AND METHODS: After taking permission from the Institutional Ethical Committee, a prospective observational case-control study was conducted in a tertiary care centre on 100 consecutive patients diagnosed with MGD. After taking informed consent, patients were assessed for the severity of MGD and correlated with risk factors.

RESULTS: The mean age of cases and controls was 53.61 ± 14.02 and 50.7 ± 13.0 years, respectively. Watering and heaviness were found to be the most common symptom in patients diagnosed with MGD. A significant correlation was observed between MGD and elderly females, contact lens wearers, smokers, diabetics, excessive use of visual display terminal, rheumatoid arthritis, use of anti-allergics, anti-hypertensive, anti-depressant, and topical anti-glaucoma drugs ($p < 0.05$). Increasing severity of MGD was associated with female sex, serum triglycerides > 150 mg/dL, total cholesterol > 200 mg/dL, serum low-density lipoprotein (LDL) > 130 mg/dL and serum high-density lipoprotein (HDL) > 40 mg/dL.

CONCLUSION: The observations in the study suggest a positive correlation between the severity of MGD and dyslipidemia, a modifiable cardiovascular risk factor. A thorough systemic workup is advisable in patients presenting to an ophthalmologist with severe MGD. Identifying and removing or modifying risk factors aggravating MGD would help alleviate their symptoms and improve their quality of life.

KEY WORDS: meibum; meibomian glands; meibomian gland dysfunction; dyslipidemia; diabetes

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INTRODUCTION

Meibomian gland dysfunction (MGD) is a chronic diffuse abnormality of the meibomian glands, characterized by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretion, which may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease [1]. Lipids secreted by the meibomian glands in the superficial lipid layer of the tear film stabilize the tear film by lowering surface tension. It also prevents evaporation of the aqueous [2]. Decrease in tear film lipids due to the destruction of glands in MGD results in increased aqueous tear evaporation, tear osmolality, and unstable tear film, leading to evaporative dry eye disease (DED) and ocular surface changes and blepharitis [3].

The prevalence of MGD ranges between 39% to 50%, with the incidence increasing with age [4, 5]. Meibomian gland dysfunction is classified into

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two categories: low delivery states (due to hyposecretion or obstruction of the ducts) and high delivery states (due to hypersecretion). Both low delivery and high delivery states of MGD are affected by endogenous factors like age, sex, hormonal disturbances, and exogenous factors like contact lens wear or topical eye drops [1]. Obstructive MGD is the most frequent variety [6]. The key factor in the pathogenesis of the development of MGD is increased viscosity of the meibum and hyperkeratinization. It results in retention of meibum within the ducts with dilatation and subsequent acing atrophy [2]. Meibomian gland (MG) secretions being lipid in nature have a possible association with systemic lipid level abnormalities. Studies show that the percentage of constituents of cholesterol in the meibum of MGD patients differs from that of healthy controls [7]. The cholesterol esters detected in secretions of the meibomian glands of patients with MGD were not always present in normal controls [8].

The objective of the present study was to identify the risk factors associated with meibomian gland dysfunction and correlate them with the severity of MGD.

MATERIAL AND METHODS

A prospective case-control observational study was undertaken after taking permission from the Institutional Ethics Committee. Patients of both sexes and above the age of 18 years, visiting the Outpatient Department of Regional Institute of Ophthalmology in Northern India with symptoms of ocular pain or fatigue, feeling of dryness or irritation, blurry vision, excessive watering or sticky discharge and/or early morning swelling around the eyes were examined. One hundred consecutive patients diagnosed with MGD and 100 age- and sex-matched controls without MGD were enrolled after taking their informed consent in their vernacular language according to the Declaration of Helsinki. Patients with recent ocular surgery, any disease related to a lacrimal drainage system, inflammatory ocular surface disease unrelated to MGD were excluded from the study.

Detailed slit-lamp biomicroscopic examination, including tear film break-up time (TBUT) testing, Schirmer test, examination of meibum expressibility and quality, was performed. The tear film break-up time was estimated by placing a fluorescein strip after wetting it with a drop of normal saline in the inferior fornix. The Schirmer test was performed without topical anesthesia. The meibum quality score (MQS) was assessed in eight glands of the central third of the lower eyelid by applying digital pressure on the lower tarsus and was graded. Meibomian glands with clear fluid were graded as 0; with cloudy fluid — as grade 1; with cloudy meibum with debris — as grade 2; and with thick toothpaste-like meibum — as grade 3. Accordingly, the meibum expressibility score was assessed from five glands of the central third of the lower eyelid. It was graded: grade 0 — with all glands expressible, grade1 — with 3–4 glands, grade 2 — with 1–2 glands, and grade 3 — with no glands expressible.

Patients were investigated for fasting blood sugar, glycated hemoglobin (HbA_{1c}), complete thyroid, and lipid profile after overnight fasting.

Meibomian gland dysfunction was divided into four stages according to the International Workshop on Meibomian Gland Dysfunction and Management (2011) [1].

- stage 1: no symptoms of ocular discomfort, itching, or photophobia with minimally altered secretions (greater than or equal to grade 2 to less than grade 4), expressibility: 1 with no ocular surface staining present;
- stage 2: minimal to mild symptoms of ocular discomfort, itching, or photophobia with minimal to mild MGD clinical signs, scattered lid margin features with mildly altered secretions (greater than or equal to grade 4 to less than grade 8), expressibility: 1 with 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 with moderate MGD clinical signs, increased lid margin features: plugging, vascularity with moderately altered secretions (greater than or equal to grade 8 to less than grade 13), expressibility: 2 with 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 with severe MGD clinical signs, increased lid margin features: dropout, displacement with severely altered secretions (grade ≥ 13), expressibility: 3 with increased conjunctival and corneal staining, including central staining (DEWS grade 24–33; Oxford grade 11–15).

Table 1. Stages of meibomian gland dysfunction (MGD) in age groups and per sex

	Controls	Cases	Stages of MGD				p-value
			1	2	3	4	
18–40 years	36 53.8%	31 46.2%	1 3.2%	11 35.5%	15 48.4%	4 12.9%	> 0.05
41–60 years	108 51.2%	103 48.8%	12 11.7%	35 34%	42 40.8%	14 13.6%	
61–80 years	56 51.9%	52 48.1%	6 11.5%	21 40.4%	21 40.4%	4 7.7%	
Male	88 52.4%	80 47.6%	4 5%	35 43.8%	35 43.8%	6 7.5%	< 0.05
Female	112 51.4%	106 48.6%	15 14.2%	32 30.2%	43 40.6%	16 15.1%	

The prevalence of risk factors in patients with MGD compared to age- and gender-matched controls were evaluated. The Chi-square test/unpaired t-test were used for qualitative variables. p-value < 0.05 was considered statistically significant in our study. All data analysis was done with IBM SPSS Statistics for Windows (IBM Corp. Version 17.0, NY, USA).

Table 2. Ocular symptoms associated with meibomian gland dysfunction

Symptoms	Cases	Control
Itching and grittiness	47	53
Redness, burning sensation and pain	44	48
Blurring of vision and photophobia	16	9
Watering and heaviness	88	54

RESULTS

One hundred consecutive patients (186 eyes) diagnosed with MGD (cases) were compared with 100 (200 eyes) age- and sex-matched controls. Fourteen eyes of cases not fulfilling inclusion criteria were excluded. In 18–40, 41–60 and 61–80 age group 46.2%, 48.8% and 48.1% cases respectively had MGD. Prevalence and severity of MGD were not observed to be significantly associated with increasing age ($p > 0.05$), while it was found to be significantly more in females as compared to males ($p < 0.05$) (Tab. 1).

Watering and heaviness were the most common symptoms associated with MGD (88 eyes), followed by itching and grittiness (47 eyes). Other symptoms included redness, burning and pain, photophobia, and blurred vision (Tab. 2).

Visual display terminal (VDT) use, smoking, contact lens usage, anti-allergic, anti-hypertensive, anti-depressant, anti-glaucoma drugs, and increased lipid profile were significantly associated with MGD compared with controls ($p < 0.05$) (Tab. 3).

Diabetes mellitus, thyroid disorder, and rheumatoid arthritis were significantly associated with MGD ($p < 0.05$) (Tab. 4).

A highly significant association was observed between increased total cholesterol (TC), serum triglyceride, low density lipoprotein (LDL), and high-density lipoprotein (HDL) and increasing severity of stage of MGD ($p < 0.001$) (Tab. 5).

DISCUSSION

Meibomian gland dysfunction is a prime cause of evaporative dry eye disease (DED). The mean age of 100 cases with MGD was 53.61 ± 14.02 years, while in the control group without MGD it was 50.7 ± 13.0 years. There was no association between increasing age and the severity of MGD ($p > 0.05$). It was similar to a study by Pinna et al. who did not find increasing age significantly associated with MGD ($p > 0.05$) [9] but was in contrast to observations by Guliani et al., who reported a strong association between increasing age and severity of stage of MGD [10].

57% of cases and 56% of controls were females. A significant association of increasing severity of MGD was observed in females ($p < 0.05$) compared to males. These results were similar to the observations by Pult et al. (2012) [11]. Guliani et al . in 2018 also reported similar findings. It could be due to the negative effect of estrogen on meibomian glands function [10]. However, Arita et al. in

Table 3. Association between meibomian gland dysfunction and risk factors

Parameters		Cases	Controls	p-value
VDT use	< 2 hours	60 61.2%	38 38.8%	0.00
	2–6 hours	43 57.3%	32 42.7%	
	> 6 hours	37 60.7%	24 39.3%	
Smoking		26 80%	10 20%	0.002
Contact lens usage		23 74.2%	8 25.8%	0.003
Anti-allergics		13 86.7%	2 13.3%	0.002
Anti-hypertensive		41 77.4%	12 22.6%	0.00
Anti-glaucoma		41 74.5%	14 25.5%	0.00
Anti-depressant		10 83.3%	2 16.7%	0.013
OCPs		2 100%	0 0%	0.141
Total cholesterol (> 200 mg/dL)		90 48.4%	36 18%	0.00

VDT — visual display terminal; OCP — oral contraceptive pills

Table 4. Association between meibomian gland dysfunction and systemic diseases

Disease	Cases	Control	p-value
Diabetes mellitus	68 69.4%	30 30.6%	0.00
Thyroid disorder	8 80%	2 20%	0.041
Systemic sclerosis	1 100%	0 0%	0.141
Steven Johnson syndrome	2 100%	0 0%	0.299
Rheumatoid arthritis	4 100%	0 0%	0.037

2008 found meibomian gland atrophy **more [missing word "prevalent"??]** in elderly males, which is probably due to the decreased beneficial effect of androgen on the meibomian gland in males above 60 years [12].

Among cases diagnosed with MGD in our study, watering and heaviness (88 eyes) were the most common symptoms, followed by itching and grittiness (47 eyes). Another study in 2016 found foreign body sensation an independent predictor of abnormal meiboscores [13].

The use of VDTs (television, mobile, computer, and laptop) in our study was observed to have a highly significant correlation with MGD ($p < 0.001$). It was in accordance with a study conducted in 2018, which also confirmed that long-term computer usage causes an evaporative dry eye disease [14]. In contrast, a study performed in

Table 5. Correlation of lipid profile with meibomian gland dysfunction (MGD)

Lipid profile	Levels	Control	Cases	MGD stage				p-value
				1	2	3	4	
Total cholesterol [mg/dL])	< 200	164 63.1%	96 36.9%	14 14.6%	42 43.8%	32 33.3%	8 8.3%	< 0.001
	> 200	36 28.6%	90 71.4%	5 5.6%	25 27.8%	46 51.1%	14 15.6%	
Serum triglyceride [mg/dL]	< 150	168 68.9%	76 31.1%	6 7.9%	39 51.3%	29 38.2%	2 2.6%	< 0.001
	> 150	32 22.5%	110 77.5%	13 11.8%	28 25.5%	49 44.5%	20 18.2%	
Low-density lipoprotein [mg/dL]	< 130	150 61.5%	94 38.5%	7 7.4%	44 46.8%	37 39.4%	6 6.4%	< 0.001
	> 130	50 35.2%	92 64.8%	12 13%	23 25%	41 44.6%	16 17.4%	
High density lipoprotein [mg/dL]	< 40	178 67.4%	86 32.6%	13 15.1%	40 46.5%	26 30.2%	7 8.1%	< 0.001
	> 40	22 18%	100 82%	6 6%	27 27%	52 52%	15 15%	

2016 validated that the MG dropout was unaffected by the frequency of computer usage [13].

Contact lens usage was found to be an important risk factor for MGD. Similar findings were also observed by Arita et al. in 2008 and Machalińska et al. in 2015 [12, 13]. A significant correlation between smoking and MGD was also observed in our study ($p < 0.001$). In 2006, Altinors et al. reported that smoking had a deteriorating effect on the lipid layer of the pre-corneal film [15]. Our finding was also supported by a study conducted in 2016 [13].

The use of anti-allergics, anti-hypertensives, anti-depressants, and topical anti-glaucoma drugs were significantly associated with MGD in our study ($p < 0.05$). Though another study performed in 2016 by Machalinska observed a significant association of MGD with the use of anti-allergic drugs but did not find any association with other drugs [13].

Several studies in the literature have documented that diabetes mellitus is related to MGD [16, 17]. We also observed a highly significant association of MGD with diabetes ($p < 0.001$), but on the contrary, a study performed in 2016 found no association of diabetes mellitus with MGD [13]. Kim et al. in 2015 confirmed the association of Graves' orbitopathy patients with obstructive type MGD [18]. The correlation of thyroid disorder with MGD in our study was also found to be statistically significant ($p < 0.05$). In contrast, no such association was observed in another study performed in 2016 [13]. We also observed a significant correlation between rheumatoid arthritis (RA) and MGD ($p < 0.05$).

71.4% of cases (90) with MGD had TC > 200 mg/dL while only 28.6% of controls (36) had TC > 200 mg/dL. Out of 90 eyes with TC > 200 mg/dL, majority (66%) eyes had stage 3 (51%) or stage 4 (15%) MGD signifying association of TC with increasing severity of MGD ($p < 0.001$). These results were consistent with the findings obtained by other authors [10, 19–21].

110 (77.5%) eyes with MGD had TGs > 150 mg/dL compared to controls where only 32 (22.5%) eyes had TGs > 150 mg/dL. The majority of the eyes (62.7%) with TGs >150 mg/dL were having stage 3 (44.5%) or stage 4 (18.2%) MGD, reflecting a highly significant association of TGs with the severity of MGD ($p <0.001$). Similar findings have also been established in the literature [10, 21, 22]. On the contrary, Dao et al. in 2010 found that the patients with MGD had a lower incidence of hypertriglyceridemia than the general population [19].

64.8% (92) of cases with MGD had LDL > 130 mg/dL whereas only 22.5% (32) of controls had LDL > 130 mg/dL. Maximum number of cases with LDL-cholesterol > 130 mg/dL had stage 3 (44.6%) or stage 4 (17.4%) MGD, sig-

nifying strong association with severity of MGD ($p < 0.001$). Similar observations have been ascertained in the other studies [10, 20, 22] whereas in contrast to this, Dao et al. in 2010 reflected no association of increased LDL with MGD [19].

82% of cases (100) with MGD had HDL > 40 mg/dL whereas only 18% of controls (22) had HDL > 40 mg/dL. The majority of the cases with HDL-cholesterol < 40 mg/dL in our study had stage 2 MGD while those with HDL-cholesterol > 40 mg/dL had stage 3 MGD suggesting a very significant association between levels of HDL (> 40 mg/dL) and increasing severity of MGD ($p < 0.001$). These results were similar to the observations made by Dao et al. in 2009 and Pinna et al. in 2013 [9, 19]. However, it is against the fact that elevated HDL has not yet been associated with any comorbidity. The cause of elevated HDL levels in such patients might be unrecognized abnormal systemic lipid processing [10]. In contrast to our findings, the studies conducted in 2017 and 2020 found no association of HDL level with the severity of meibomitis [20, 21].

CONCLUSION

In our study, the prevalence of MGD was higher in females, diabetics, contact lens wearers, smokers, visual display terminal excessive users, patients with hypothyroidism, rheumatoid arthritis, and patients using anti-allergic, anti-hypertensive, anti-depressant, and topical anti-glaucoma drugs. A strong association was observed between the severity of MGD and increased triglycerides, total cholesterol, LDL, and HDL. Therefore, a thorough systemic workup is desirable in patients presenting to an ophthalmologist with severe MGD. Identification and removal or modification of risk factors aggravating MGD would help alleviate symptoms and improve patients' quality of life.

Limitations

The sample size in our study was small and advanced technologies like K-5 meibography to assess the morphology of the meibomian gland were not available in our centre.

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Nil.

Conflict of interests

Nil.

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