MEIBOMIAN GLAND DYSFUNCTION AND HYPERCHOLESTEROLEMIA- A REVIEW ARTICLE

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What is meibomian gland dysfunction?

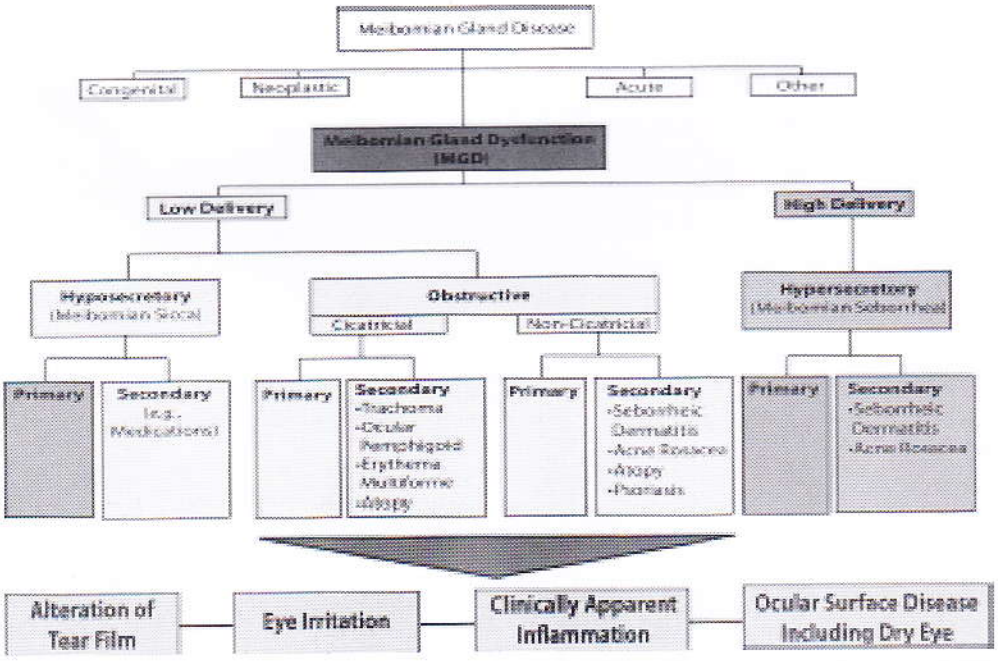
Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/ quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.

Dysfunction-function of meibomian gland is disturbed. Diffuse-most of the glands involved. Obstruction of meibomian gland orifices and terminal ducts and qualitative or quantitative changes in gland secretion is the most prominent aspect of MGD. Subjective symptoms of eye irritation are included in the definition.

Meibomian gland disease is used to describe a broader range of meibomian gland disorders like neoplasia and congenital disease. Other terms such as meibomitis or meibomianitis describe a subset of disorders of MGD associated with inflammation of the meibomian glands. Although inflammation may be important in the classification and in the therapy of MGD, these are not sufficiently general, as inflammation is not always present.

Hypercholesterolemia (total cholesterol _200 mg/dl) is a significant risk factor for ischemic heart, cerebrovascular, and peripheral vascular disease. Increased cholesterol in the glandular secretion has been postulated to be necessary for the development of meibomian gland dysfunction (MGD), a common form of chronic blepharitis.

CLASSIFICATION OF MGD (TABLE 1)[16]



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Epidemiologic studies have firmly established abnormal lipid levels as significant risk factors for cardiovascular disease [1-3] and stroke [4-5]—some of the leading causes of mortality in the developed world [6-7].

Emerging studies [8] have linked increased cholesterol esters in meibomian secretions to patients with meibomian gland dysfunction (MGD). Meibum with higher cholesterol composition has a higher melting point [9], which is postulated to result in more viscous secretions that may then obstruct meibomian glands or alter the quality of posterior eyelid excreta. Furthermore, patients with moderate to severe MGD seem to have a higher prevalence of abnormal serumcholesterol levels versus the general public [10-12]. MGD is a common cause of ocular surface disease,[13-14] yet its impact on patients' overall health is often overlooked [15]. Eye care providers may be the first to detect systemic diseases such as cerebrovascular disease because of their initial ocular manifestations (e.g., amaurosis fugax & retinal vascular occlusion). Retinal vascular occlusions are just one example of how the ophthalmic exam could providemclues about the presence of systemic disease. A known risk factor for cardiovascular illness is dyslipidemia. This term encompasses several abnormalities in the serum lipid profile such as a total cholesterol C200 mg/dL, triglycerides C150 mg/dL, low-density lipoprotein (LDL) C130 mg/dL, or high-density lipoprotein (HDL) B40 mg/dL [10-12,15].

Pathophysiology of MGD

Meibomian gland dysfunction is caused primarily by terminal duct obstruction with thickened opaque meibum containing keratinized cell material. The obstruction, in turn, is due to hyperkeratinization of the ductal epithelium and increased meibum viscosity. The obstructive process is influenced by endogenous factors, such as age, sex, and hormonal disturbances, as well as by exogenous factors such as topical medication. Meibomian gland dysfunction is caused primarily by terminal duct obstruction with thickened opaque meibum containing keratinized cell material. The obstruction, in turn, is due to hyperkeratinization of the ductal epithelium and increased meibum viscosity. The obstructive process is influenced by endogenous factors, such as age, sex, and hormonal disturbances, as well as by exogenous factors such as topical medication. The obstruction may lead to intraglandular cystic dilatation, meibocyte atrophy, gland dropout, and low secretion, effects that do not typically involve inflammatory cells. The outcome of MGD is a reduced availability of meibum to the lid margin and tear film. The consequence of insufficient lipids may be increased evaporation, hyperosmolarity and instability of the tear film, increased bacterial growth on the lid margin, evaporative dry eye, and ocular surface inflammation and damage.

Table 2: Population based study providing estimates of prevalence of mgd[16]

Study	Participants	Ethnicity	Parameter	Prevalence (%)	Age (y)
Beijing Eye Study	1957	Mainland Chinese	Telangiectasia (asymptomatic) Telangiectasia (symptomatic of dry eye)	68 69.3	>40
Japanese study	113 pensioners	Japanese	Gland dropout, expressibility and nature of meibum secretion	61.9	>60
Shihpai Eye Study	1361	Taiwanese Chinese	Telangiectasia or meibomian gland orifice plugging	60.8	>65
Melbourne Visual Impairment Project	926	Caucasian	Tear break up time <1 SD (10 s) Tear break up time <1.5 SD (8 s)	19.9 8.6	40–97
Salisbury Eye Evaluation	2482	Caucasian	Meibomian gland plugging or collarettes (grades 2 and 3)	3.5	>65

Correlation with Altered Lipid Profile:

Patients with moderate to severe mgd have increased levels of total cholesterol compared to population controls. Increased cholesterol at the glandular secretion level has been studied and hypothesized to be a factor in meibomian gland dysfunction.[17,20] Because normal whole meibomian lipids have a melting point of 30°C to 34°C[18] and cholesterol has a melting point of 148°C,[18] increased concentration of cholesterol in meibomian lipid would increase the melting point of the meibomian lipid milieu, theoretically increasing viscosity and leading to plugging of the meibomian glands.[17] The composition of normal meibum secretions has been well studied and cholesterol content has been reported to be 1% to 2%[19] however, to our knowledge, meibum composition in patients with meibomian gland dysfunction has not been studied.

One study attempted to associate serum cholesterol and human tear fluid and found that cholesterol concentration in the tear film bore no correlation to serum cholesterol.[21] However, this research measured the concentration of cholesterol in the aggregate tear film. It did not measure this concentration in the lipid layer, in the meibum, or in the meibomian gland. Altered meibomian lipid concentration, including an increase in meibum cholesterol, has been shown to cause dry eye symptoms. In another study, patients on antiandrogen therapy were found to have an altered meibomian lipid composition with a notable increase in the quantity of cholesterol.[20] These patients experienced a subjective increase in dry eye symptoms, including light sensitivity, painful eyes, and blurred vision. Under biomicroscopy, the patients were found to have an increase in tear film debris, the presence of an abnormal tear film meniscus, irregular posterior lid margins, increased vital dye stain, conjunctival injection, and a significantly decreased tear break-up time, all signs of dry eye disease.[20] Furthermore, it has been shown that patients with Sjögren syndrome have increased cholesterol content in their tear film.

More studies, both prospective and at the basic science level, will be needed to examine the significance of this finding.

Stage	MGD Grade	Symptoms	Corneal Staining
1	+ (minimally altered expressibility and secretion quality)	None	None
2	++ (mildly altered expressibility and secretion quality)	Minimal to mild	None to limited
3	+++ (moderately altered expressibility and secretion quality)	Moderate	Mild to moderate; mainly peripheral
4	++++ (severely altered expressibility and secretion quality)	Marked	Marked; central in addition
"Plus" disease	Co-existing or accompanying disorders of the ocular surface and/or eyelids		

Diagnosis of MGD

Clinical examination:

1. Assessment of blink rate and intrtblink interval: normal is 14-18 timesper minute.

2. Examination of eyelid and its margfin:compromised eyelid margin like tylosis,entropion,ectropion,trichiasis,dydtichiasis can predispose to mgd.also surrounding skin features of rosacea like telangiectasia is an important precursor of mgd.the meibomian gland duct orifices are assessed whether open or capped.

3. Assessment of Tear Film: Normal meniscus height is more than 0.25mm.

4.Tear film break up time: On fluorescein staining normal time taken for tear film to break is more than 10 seconds. TBUT of >10 sec is suggestive of dry eye. The stability is largely dependent on lipid layer that is secreted by meibomian glands but it can also be altered in aqueous deficient dry eye. Therefore TBUT cannot differentiate between MGD AND DED .

5. Ocular Surface Staining: Cornea best assessed with fluorescein and conjunctiva is best assessed with lissamine green.the staining pattern has been given a clinical score that is useful for diagnosis and follow up management. Most commonly used scoring system is NEI(national eye institute)grading system.

6. Meibomian gland expression: Expressibiliy is assessed along with nature of meibum.

Investigations

These can be divided into-

1. Routine tests

2. Specialized tests

Routine Tests: These are done in a specific order to minimize the extent to which one test may influence the other.the recommended sequence is as follows:

Symptom questionnaire

Blink rate and blink interval-blink rate is number of blinks in one minute

Blink interval is calculated by 60/blink rate

Tear meniscus height: can be calculated with or without fluorescein instillation. Normal is between 0.2-0.3mm(1,2). TMH is measured as the distance between the darker edge of the lower eyelid and the top of reflex from tear strip.

Tear film osmolarity: Osmolarity is graded within ranges of mOsmls/l: normal-(275-300), mild-(303-310), moderate(320-335) and severe (350)

Instillation of fluorescein and measurement of TBUT and Ocular protection index: TBUT is defined as interval between last blink and the appearance of first randomly appearing black spot. It is affected in lipid layer deficiency .So it is a good indicator of dry eye in mgd even though it may be affected in aqueous deficiency dry eye. A TBUT of <10 seconds is considered abnormal.

Grading of corneal and conjunctival fluorescein staining: Various grading systems have been proposed like NEI(national eye institute)grading and Bijstervald grading. It has been reported that staining along upper and lower lid margins is more likely to be associated with MGD or some form of blephritis and central staining is more associated with aqueous deficient dry eye.[2]

Lid examination and expression

Meibography: This technique is developed solely for directly observing the morphology of meibomian glands in vivo.

Schirmer's test: This should be the final test to be done as it may affect other staining tests. A score of <5mm in 5 minutes is an indicator of severe dry eye.

Specialized Tests

Interferometry: This technique is used to analyse lipid layer. The most recent invention is Lipiview interferometer which uses white light interferometry to form a pattern that is termed interferogram.

Invivo confocal microscopy (ICVM): It is a contact procedure that has been evaluated for meibomian gland examination. It can be used to assess acinal density and diameter, secretion reflectivity and peri glandular inflammation in patients with MGD. It can be also be used to make the resistant demodex mites in the meibomian gland orifices.

Management of MGD

Management of MGD is based on the staging of the disease.

Stage 1

Inform patient about MGD, the potential impact of diet, and the effect of work/home environments on tear evaporation, and the possible drying effect of certain systemic medications. *Consider* eyelid hygiene including warming/expression.

Stage 2

Advise patient on improving ambient humidity; optimizing workstations and increasing dietary omega-3 fatty acids intake.

Institute eyelid hygiene with eyelid warming (a minimum of four minutes at 40-45 degrees celsius, once or twice daily) followed by moderate to firm massage and expression of MG secretions.

'Lipiflow' treatment- warms the internal surface of both lids and massages the lids.

Artificial lubricants, topical azithromycin.

Stage 3

Oral tetracycline derivatives should be considered along with above mentioned methods.

Stage 4

Anti-inflammatory therapy for dry eye along with above methods like - Cyclosporine A (has an immunomodulating effect on T lymphocytes) 5% N-acetylcysteine (has mucolytic, anti-collagenolytic, and antioxidant properties).

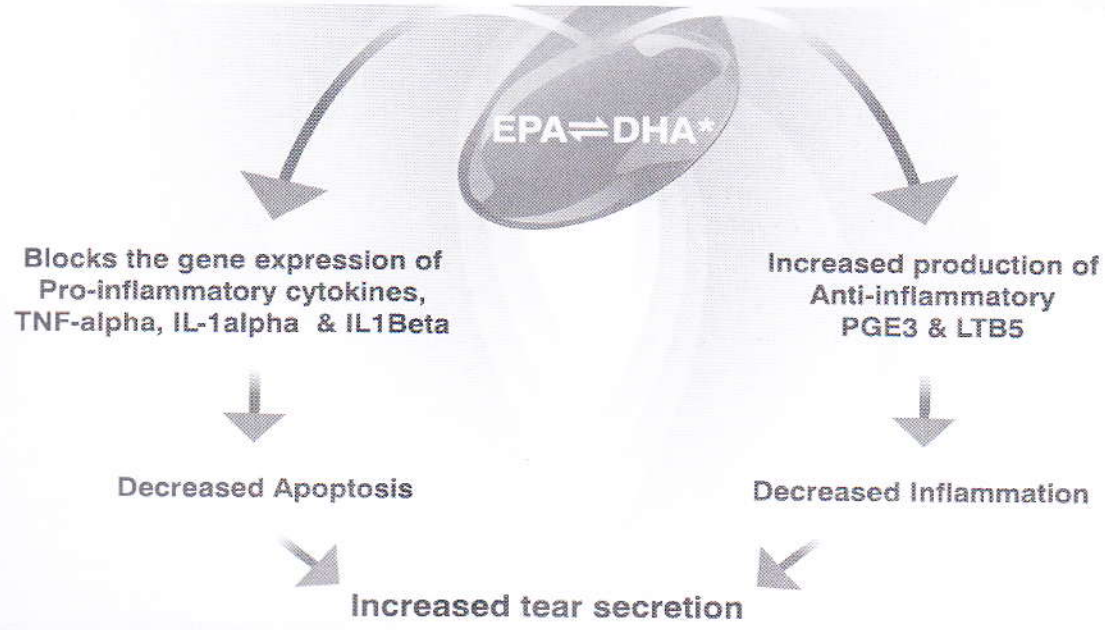
Steroids are used only for acute exacerbations or topically for the treatment of marginal hypersensitivity keratitis.

Probing mechanically opens and dilates the orifices and ducts of the meibomian glands, provided scarring has not caused irreversible damage. This facilitates a free flow of meibum.

Role of tetracycline:

1. Suppresses migration of leucocytes and inflammatory cytokines
2. Reduces production of nitric oxide and reactive oxygen species which play a role in the build up of inflammation.
3. Inhibition of matrix metalloproteinase .
4. Inhibition of phospholipase A2 which in turn inhibits bacterial endotoxins.
5. Reduces levels of irritative fatty acids and diglycerides by suppressing bacterial lipases.
6. Antimicrobial activity leads to reduction in number of vital bacteria.
7. Inhibition of keratinization

Role of omega 3 fatty acids:



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