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Prevalence of dry eye disease and its association with dyslipidemia

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Abstract

Background: Dry eye disease (DED) is a common ocular surface disease significantly affecting the quality of life of patients. The aim of our study is to focus on the prevalence of DED and to determine the relationship between dyslipidemia and DED.

Methods: The study was performed with the age group of 25–70 years, who attended the ophthalmology outpatient department at Sri Lakshmi Narayana Institute of Medical Sciences with complaints of dry eye. A standard questionnaire was taken, and tear film tests were performed to diagnose dry eye. Further eyelid margin was examined to detect meibomian gland dysfunction. Based on the tests and examination, patients were grouped as men with and without DED and women with and without DED. Fasting lipid profile was investigated for these groups.

Results: The study showed the prevalence of DED mainly in women and found significant association between DED and dyslipidemia. There is a significant relationship between total cholesterol and DED groups especially in women ($p < 0.001$). We also found the association between triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol and DED particularly in women as compared to men.

Conclusions: Based on the findings, we emphasize that there is a strong relationship between dyslipidemia and the progression of DED particularly in women. Ophthalmologists may increase their role to educate themselves to diagnose dyslipidemia and ensure comprehensive eye care to prevent blindness and cardiovascular disease. Recent treatment modalities could be aimed to improve the quality of life of women and elderly patients suffering from DED.

Keywords: dry eye disease; dyslipidemia; lipid profile; meibomian gland dysfunction.

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Introduction

Lipids are key components of the tear film, which maintains a smooth corneal surface and prevents premature evaporation of tears from the ocular surface of the eye [1]. The tear film lipid layer is mainly released by the meibomian glands, which are tubuloacinar holocrine glands that discharge their entire contents during the secretion process [2]. As normal meibomian gland secretion is lipid in nature, chemical analysis showed that it consists of a mixture of non-polar lipids (77% wax and sterol esters), polar lipids (8% phospholipids and glycolipids) and 9% diglycerides and triglycerides (TG), and this distribution varies with variations in melting point [3].

A series of epidemiologic studies established that abnormal lipid levels are one significant risk factor for cardiovascular disease (CVD) [4–6]. Emerging studies showed association between increased cholesterol esters in meibomian secretions of patients with meibomian gland dysfunction (MGD) [7, 8]. Furthermore, higher prevalence of abnormal serum cholesterol levels was reported in MGD patients [9–11]. MGD is a major cause of dry eye but is often not noticed by people with their busy schedules. It has been suggested that disturbances in lipid metabolism resulting from systemic and environmental conditions, such as lifestyle changes, westernized diet and medications, computer usage and hormonal status increase the incidence and prevalence of dry eye disease (DED) in the general population [8].

Moss et al. [12] reported that based on the Beaver Dam population-based study, the prevalence of DED rate was 14% in adults of age 48–91 years, and more women are affected with DED than men (16.7% vs. 11.4%, respectively). Epidemiological studies from the large Women's Health Study and Physician's Health Study indicate that the prevalence of symptomatic dry eye in the US is about 7% in women, which corresponds to 3.2 million, and 4% in men corresponding to 1.05 million over the age of 50 years with DED [13, 14]. The prevalence of DED was also reported in countries like Australia, Canada, Indonesia, Taiwan and Japan.

As DED is increasing and recognized as a serious, worldwide public health concern, it is necessary to study about MGD, its causes, early diagnosis and detection with possible treatment options. Patients with symptoms of dry eye and clinical findings like arcus senilis and xanthelasma (indicators of high cholesterol in the body) account for a large number of ophthalmologist consultations. Hence, it provokes ophthalmologists to investigate the association between lipid profile and DED. We intended, therefore, to focus on the following: (1) the prevalence of DED and (2) checking if there is any association between serum lipid profile and DED and its interpretation regarding early detection and treatment.

Materials and methods

The study was conducted in the Department of Ophthalmology in collaboration with Department of Biochemistry, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry from March 2016 to August 2016. A hundred patients were selected randomly in the age group of 25–70 years. Of them were 60 cases of clinically diagnosed DED, and 60 age- and sex-matched healthy subjects were taken as controls. The study was approved by the Institutional Human Ethical Committee. Informed consent was obtained from all the patients recruited for the study.

Patients with dry eye symptoms were included for the study. Patients with compliance of diabetes, using antihypertensive drugs, ocular surface disorders, allergic conjunctivitis and disorder of eye lid and previous history of any ocular surgery were excluded from the study.

Evaluation of dry eye

Patients having symptoms suggestive of dry eye were evaluated. A detailed medical history and direct interviews with patients were taken using a questionnaire. Clinical examination like tear break-up time [t-BUT] and Schirmer's test with 5 × 35 mm strip of Whatman-41 filter paper was performed to confirm the diagnosis and grading of dry eye. Based on the test results, the dry eye patients were graded into three groups: mild, moderate and severe DED, and the prevalence in gender was noticed.

Dry eye patients were further evaluated by slit lamp biomicroscopy for blepharitis and the degree of MGD. After complete ocular examination, patients were grouped as men without DED, men with DED, women without DED and women with DED.

Sample preparation

Blood samples were collected from all individuals. About 5 mL of blood was withdrawn from overnight-fasted individuals. Plasma and serum were separated from blood sample for the measurement of blood sugar and lipid profile.

Biochemical estimations

Fasting blood sugar was estimated by glucose oxidase peroxidase method. Serum TG and total cholesterol (TC) were measured by glycerol 3 phosphate oxidase N-ethyl sulfopropylanisidine and cholesterol oxidase-peroxidase end point methods, respectively. Serum high density lipoprotein (HDL) was estimated by enzyme selective protection method. Serum low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were calculated using Friedwald's formula (LDL = TC – HDL – TG/5).

Statistical analysis

Data analysis was performed using SPSS statistical software (version 22, SPSS, Inc., Chicago, IL, USA). The results were presented as mean ± SD. Chi square test was performed to find out the significant difference between the groups. Mean values of Table 6 were compared using Student's t-test. A value of $p < 0.05$ was considered statistically significant.

Results

Table 1 shows the relationship between age and DED. Aging is one of the risk factors for the progression of DED. Among 60 DED cases, we found 21.6% of DED in the group age of 25–35 years and 36.6% and 41.6% in the age groups of 35–50 and 51–70, respectively.

Table 1: Age vs. DED prevalence.

Age, years	DED (n = 60)		Total	Percentage of people affected with DED, %
	Total no. of men (n = 23)	Total no. of women (n = 37)		
25–35	6	7	13	21.6
36–50	9	13	22	36.6
51–70	8	17	25	41.8
Total	23	37	60	–

DED, dry eye disease.

The study was carried out with 60 DED cases and 60 non-DED cases as controls. Of 60 cases, 23 men and 37 women were in the group with DED, whereas 25 men and 35 women were in the group without DED. Of 60 patients, we found 30.4% with mild DED cases, 43.4% with moderate DED and 26% with severe DED in men, and in women they were 25%, 46% and 30%, respectively, representing significant correlation between grading and prevalence of DED (Table 2).

As MGD is the leading cause of DED, the present study assessed the same in DED patients. Out of 60 DED patients, 16 (26.6%) had mild disease, 27 patients (45%) had moderate disease, and 17 patients (28.3%) showed a severe degree.

Among 60 patients with grades of DED, 40 (66.7%) patients of both sexes had meibomian gland disease. The higher number (n=28) was noted in females, and it amounted to 46.7% as compared to males (20%) with DED having meibomian gland disease (Tables 3 and 4).

Serum lipid profile between genders and its association with and without DED are given in Table 5. Both men and women in the DED groups showed statistically significant association with dyslipidemia as compared to groups without DED, with women having statistically higher prevalence than men.

Mean values of fasting lipid profile of DED groups are presented in Table 6. The study showed a strong significant association between DED and elevated total cholesterol levels in women when compared to men. Similarly, we found increased levels of TG and altered lipoprotein profile [increased low density lipoprotein cholesterol (LDL-C) and decreased high density lipoprotein cholesterol (HDL-C)] in women, which were highly significant as compared to men, indicating that dyslipidemia is predominant in women.

Table 2: Frequency of grades of DED in men and women.

Grading of dry eye	Men	Percentage of DED, %	Women	Percentage of DED, %	p-Value
Mild	7	30.4	9	25	0.038
Moderate	10	43.4	17	46	
Severe	6	26	11	30	
Total no. of cases	23	–	37	–	

χ^2-Test was performed to find out the gender-wise prevalence of DED. $p<0.05$ was considered statistically significant. DED, dry eye disease.

Table 3: Association between MGD and severity of DED.

MGD	DED (n=60)					
	Mild (n=16)		Moderate (n=27)		Severe (n=17)	
	Male (n=7)	Female (n=9)	Male (n=10)	Female (n=17)	Male (n=6)	Female (n=11)
Present	4	6	6	13	2	9
Absent	3	3	4	4	4	2
Total	7	9	10	17	6	11

MGD, meibomian gland dysfunction; DED, dry eye disease.

Table 4: Correlation between MGD and DED.

MGD	DED (n=60)					p-Value
	Men	%	Women	%	Total	
Present	12	20	28	46.7	40 (66.7%)	0.032
Absent	11	18.3	9	15	20 (33.3%)	
Total	23	–	37	–	60	

χ^2-Test was performed to find out the correlation between MGD and severity of DED. $p<0.05$ was considered statistically significant. MGD, meibomian gland dysfunction; DED, dry eye disease.

Discussion

Dry eye is a disorder of the tears and ocular surface which is presented with symptoms of irritation, sandy sensation, feeling of dryness, itching and non-specific ocular discomfort. Meibomian glands contribute to the lipid component of the tear film and prevent the evaporation of the tear film [15]. A study reported that disruption or deficiency of the tear film could cause increased stress on the ocular surface which in turn leads to DED, and if it is left untreated, it might result in perforation of the cornea, visual impairment and blindness [16].

The alteration of tear film lipid content due to MGD can cause tear film instability, which in turn presents as dry eye symptoms. Several risk factors for the development of DED have been identified frequently in epidemiological studies such as increasing age and female sex. Koumi study documented the prevalence of DED of 12.5% in men and 21.6% in women [17]. Further studies showed that changes in sex hormones in women between the ages of 40 and 50 years might alter meibomian gland secretion [18, 19]. Clinically menopausal and postmenopausal women both tend to have dry eye symptoms, which can be attributed to the significant decrease of tear production [20]. In support of the above literature, the present study observed 36.6% and 41.8% of DED in the age groups of 36–50 and 56–70 years, respectively, and its frequency is gradually increasing in women representing one of the risk factors for DED development.

Table 5: Serum lipid profile between genders with and without DED.

Parameters	Men		p-Value	Women		p-Value
	Non-DED (n=25)	DED (n=23)		Non-DED (n=35)	DED (n=37)	
Triglycerides < 200 mg/dL	20	9	p < 0.004[a]	28	12	p < 0.003[a]
Triglycerides > 200 mg/dL	5	14		7	25	
Total cholesterol < 200 mg/dL	19	5	p < 0.002[a]	25	7	p < 0.001[b]
Total cholesterol > 200 mg/dL	6	18		10	30	
HDL-C < 35 mg/dL	21	15	p < 0.004[a]	11	25	p < 0.003[a]
HDL-C > 35 mg/dL	7	8		24	12	
LDL-C < 130 mg/dL	18	9	p < 0.028[a]	26	14	p < 0.002[a]
LDL-C > 130 mg/dL	7	14		9	23	
VLDL-C < 40 mg/dL						
VLDL-C > 40 mg/dL	21	18	p = 0.611	30	30	p = 0.59

χ^2-Test was performed to find out the significant difference between groups with and without DED. [a]p < 0.05 was considered statistically significant. [b]p < 0.001 was considered statistically highly significant. DED, dry eye disease; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol.

Table 6: Fasting lipid profile of men and women with DED.

Parameters	Men	Women	SD error	p-Value
Triglycerides > 200 mg/dL	243 ± 15.58	328 ± 18.1	5.643	0.0001[b]
Total cholesterol > 200 mg/dL	275 ± 16.58	363 ± 19.05	5.419	0.0001[b]
HDL-C < 35 mg/dL	38 ± 6.16	29 ± 5.38	3.237	0.0103[a]
LDL-C > 130 mg/dL	152 ± 12.3	171 ± 13.07	4.335	0.0001[b]

Values are expressed as mean ± SD. Student's t-test was used as a test of significance for comparison between men and women with DED. [a]p < 0.05 was considered statistically significant. [b]p < 0.0001 was considered statistically highly significant. DED, dry eye disease; SD, standard deviation; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

The relationship between MGD and ocular surface disease such as dry eye leading to subsequent surface irritation and inflammation was well established. In the present study, association between MGD and DED was assessed, and it was found among 66.7% of both male and female patients. In women, 46.7% showed presence of MGD, whereas 20% men showed presence of MGD, indicating that the presence of meibomian gland disease and frequency of DED was high in females. Finis et al. [21] reported that MGD causing DED affects women more often than men and its incidence increases with age and is influenced by the hormonal status.

It is well suggested that hypercholesterolemia could be seen in the presence of DED as increased cholesterol in the meibomian lipid would increase its melting point to 46 °C versus the normal meibomian lipid melting point of 30–34 °C and, thus, lead to increased viscosity and plugging of the meibomian orifice [22]. Chun et al. [23] reported that female patients with DED had a statistically higher prevalence of hypercholesterolemia and pertained to MGD. Further higher incidence of dyslipidemia, in particular higher TC, was observed in case-control study of meibomian gland disease, a key cause of evaporative DED [9]. Pinna et al. [10] reported elevated blood cholesterol levels in MGD group compared to control group, and there was a strong significant association with MGD. Braich et al. [7] showed elevated cholesterol levels in MGD patients and proved a close relationship between dyslipidemia and MGD. Consistent with the aforementioned literature, we found increased prevalence of hypercholesterolemia in women with DED than in men.

Similar as well as dissimilar results were found in recent studies. Dao et al. [9] reported that in MGD patients HDL was the major component contributing to the elevated total blood cholesterol level. Interestingly, we found low HDL-C which was more prevalent in DED cases than non-DED; in particular, female with DED showed statistically significant values when compared to males. HDL, which is well known for its preventive effect in CVD, may act negatively in the presence of DED. Adding support to our study, Jasmine Mary et al. [8] reported lower levels of HDL along with the association between dyslipidemia and MGD.

Conclusions

DED is a prevalent, multifactorial disease that is common in women and elderly patients. Based on the findings of the study, we emphasize that there is a strong relationship between lipid profile and the progression of DED which affects women particularly. This might be due to lifestyle modifications, frequent exposure to allergens, computer usage and mainly hormones like estrogen and testosterone levels that influence MGD; this may require further study. Small sample size is one of the limitations of our study which can be carried out on a large population in order to prove the underlying association between dyslipidemia and MGD. Very recently, the relationship between dyslipidemia and MGD with respect to DED has been proven, and this corroborates our findings. However, further studies are needed in order to confirm the underlying mechanism in the association between DED and dyslipidemia. Ophthalmologists may increase their role for early detection of dyslipidemia in DED patients to ensure comprehensive eye care to prevent blindness and CVD. Recent treatment modalities could be aimed at improving the quality of life of women as well as of elderly patients suffering from DED. Prevention and development of awareness of DED among the public may improve the quality of life.

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References

1. Bron AJ, Tiffany JM, Gouveia SM, Yokoi N, Voon LW. Functional aspects of the tear film lipid layer. Exp Eye Res 2004;78: 347–60.
2. Butovich IA. Lipidomics of human meibomian gland secretions: chemistry, biophysics, and physiological role of meibomian lipids. Prog Lipid Res 2011;50:278–301.
3. Nicolaides N, Kaitaranta JK, Rowdah TN, Macy JI, Boswell FM, Smith RE. Meibomian gland studies: comparison of steer and human lipids. Invest Ophthalmol Vis Sci 1981;20:522–36.
4. Sherpa LY, Deji Stigum H, Chongsuvivatwong V, Luobu O, Thelle DS, Nafstad P, et al. Lipid profile and its association with risk factors for coronary heart disease in the highlanders of Lhasa, Tibet. High Alt Med Biol 2011;12:57–63.
5. Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease. Prim Care 2013;40:195–211.
6. Muntner P, Colantonio LD, Cushman M, Goff DC Jr, Howard G, Howard VJ, et al. Validation of the atherosclerotic cardiovascular disease pooled cohort risk equations. J Am Med Assoc 2014; 311:1406–15.
7. Braich PS, Howard MK, Singh JS. Dyslipidemia and its association with meibomian gland dysfunction. Int Ophthalmol 2016;36:469–76.
8. Jasmine Mary J, Simi SP, Goudinho SJ. The association of meibomian gland dysfunction with dyslipidemia – a case-control study. World J Pharm Res 2016;5:1390–6.
9. Dao AH, Spindle JD, Harp BA, Jacob A, Chuang AZ, Yee RW. Association of dyslipidemia in moderate to severe meibomian gland dysfunction. Am J Ophthalmol 2010;150:371–5.
10. Pinna A, Blasetti F, Zinellu A, Carru C, Solinas G. Meibomian gland dysfunction and hypercholesterolemia. Ophthalmology 2013;120:2385–9.
11. Bukhari AA. Associations between the grade of meibomian gland dysfunction and dyslipidemia. Ophthal Plast Reconstr Surg 2013;29:101–3.
12. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. Arch Ophthalmol 2000;118:1264–8.
13. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol 2003;136:318–26.
14. Schaumberg DA, Sullivan DA, Dana MR. Epidemiology of dry eye syndrome. Adv Exp Biol Med 2002;506:989–98.
15. Lemp MA, Foulks GN. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop 2007. Ocul Surf 2007;5:75–92.
16. Nichols KK. The international workshop on meibomian gland dysfunction: introduction. Invest Ophthalmol Vis Sci 2011;52:1917–21.
17. Uchino M, Nishiwaki Y, Michikawa T, Shirakawa K, Kuwahara E, Yamada M, et al. Prevalence and risk factors of dry eye disease in Japan: Koumi study. Ophthalmology 2011;118:2361–7.
18. Sullivan DA, Sullivan BD, Evans JE, Schirra F, Yamagami H, Liu M, et al. Androgen deficiency, meibomian gland dysfunction, and evaporative dry eye. Ann N Y Acad Sci 2002;966:211–22.
19. Yazdani C, McLaughlin T, Smeeding JE, Walt J. Prevalence of treated dry eye disease in a managed care population. Clin Ther 2001;23:1672–82.
20. Lambert DW, Foster CS, Perry HD. Schirmer test after topical anesthesia and the tear meniscus height in normal eyes. Arch Ophthalmol 1979;97:1082–5.
21. Finis D, Schrader S, Geerling G. [Meibomian gland dysfunction]. Klin Monbl Augenheilkd 2012;229:506–13.
22. Butovich IA, Millar TJ, Ham BM. Understanding and analyzing meibomian lipids – a review. Curr Eye Res 2008;33:405–20.
23. Chun YH, Kim HR, Han K, Park YG, Song HJ, Na KS. Total cholesterol and lipoprotein composition are associated with dry eye disease in Korean women. Lipids Health Dis 2013;12:84.