Association of Dry Eye Disease With Dyslipidemia and Statin Use

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• PURPOSE: To determine whether an association exists between dry eye disease (DED) and statin use and/or dyslipidemia.
• DESIGN: Retrospective, case-control study.
• METHODS: SETTING: University of North Carolina (UNC)-affiliated healthcare facilities. STUDY POPULATION: 72,931 patients seen at UNC ophthalmology clinics over a 10-year period. MAIN OUTCOME MEASURES: Odds ratios (ORs) calculated between DED and a history of low, moderate, or high-intensity statin use; and ORs calculated between DED and abnormal lipid panel values.
• RESULTS: Total of 39,336 individuals (53.9% female) were analyzed after exclusion of individuals with confounding risk factors for DED. Of these, 3,399 patients (8.6%) carried a diagnosis of DED. Low-, moderate-, and high-intensity statin regimens were used by 751 subjects (1.9%), 2,655 subjects (6.8%), and 1,036 subjects (2.6%). Lipid abnormalities were identified as total cholesterol >200 mg/dL, 4,558 subjects (11.6%); high-density lipoprotein (HDL) <40 mg/dL, 2,078 subjects (5.3%); low-density lipoprotein (LDL) >130 mg/dL, 2,756 subjects (7.0%); and triglycerides (TGs) >150 mg/dL, 2,881 subjects (7.3%). The odds ratios (OR) of carrying a diagnosis of DED given the presence of low-, moderate-, and high-intensity statin use were 1.39 (95% confidence interval [CI]: 1.13-1.72); OR 1.47 (95% CI: 1.30-1.65), and OR 1.46 (95% CI: 1.21-1.75), respectively. The OR of carrying a diagnosis of DED given the presence of total cholesterol >200 mg/dL, HDL <40 mg/dL, LDL >130 mg/dL, and TGs >150 mg/dL were 1.66 (95% CI: 1.52-1.82), 1.45 (95% CI: 1.26-1.67), 1.55 (95% CI: 1.39-1.74), and 1.43 (95% CI: 1.27-1.61), respectively.
• CONCLUSIONS: A history of statin use or dyslipidemia is associated with an increased odds of having a DED diagnosis. Further studies are needed to determine whether statin use and/or dyslipidemia increases the risk of DED. (Am J Ophthalmol 2020;218:54–58. © 2020 Elsevier Inc. All rights reserved.)

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DRY EYE DISEASE (DED) AFFECTS A SIGNIFICANT proportion of the general population, with an estimated prevalence ranging from 7% to 33%.[1–3] The incidence and severity of DED increases with age and female sex.[1] This multifactorial condition is characterized by decreased tear production and/or increased evaporation and can lead to symptoms of ocular discomfort, visual disturbances, and a diminished quality of life.[4,5] Meibomian gland dysfunction (MGD) is the most common cause of evaporative dry eye[6] and involves abnormalities in the quantity and/or composition of tear film lipids, including excess free cholesterol.[7] The relationship between systemic lipid abnormalities and those of the tear film has not been clearly established.[8] However, prior studies, although conflicting, suggest an association between MGD/DED and dyslipidemia.[9–13]

Dyslipidemia is a significant risk factor for cardiovascular disease, affecting an estimated 12% of adults.[14] It is most often treated with "statin" medications.[15] This drug class is composed of β-hydroxy β-methylglutaryl-co-enzyme A (HMG-CoA) reductase inhibitors, which block the rate-limiting step in the biosynthesis of cholesterol.[16] HMG-CoA reductase expression has been identified within the sebaceocytes of meibomian glands in human eyelid tissue.[16] Thus, it is possible that statin use could alter cholesterol synthesis and lipid homeostasis within the meibomian glands, leading to destabilization of the tear film and subsequent DED.

To investigate a potential association between DED and each of a history of statin use or dyslipidemia, this study examined a large number of patients seen at University of North Carolina (UNC)-affiliated healthcare facilities over a 10-year period.

SUBJECTS AND METHODS

THIS WAS A RETROSPECTIVE CASE-CONTROL STUDY WITH approval obtained from the institutional review board of UNC. All methods described herein adhered strictly to the tenets of the Declaration of Helsinki and Health

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Insurance Portability and Accountability Act regulations. The dataset was acquired from the Carolina Data Warehouse for Health (CDWH), a repository of de-identified patient information collected from patient visits at UNC-affiliated hospitals and outpatient clinics. Use of an online interface linked to the CDWH identified 72,931 unique patients older than 18 years of age, with prior lipid panel results, and seen at UNC ophthalmology clinics between May 1, 2008, and May 31, 2018.

Queries were performed to identify unique individuals among this group carrying a diagnosis of DED (International Classification of Diseases, ed. 9 [ICD-9] and ICD-10 codes 370.33, 375.15, H04.12x, and H16.22x). Additional queries were carried out to identify patients with a history of low-intensity, moderate-intensity, and high-intensity statin use as well as those with dyslipidemia. Low-intensity statins included fluvastatin, 20-40 mg daily; lovastatin, 20 mg daily; pitavastatin, 1 mg daily; pravastatin, 10-20 mg daily; and simvastatin, 10 mg daily. Moderate-intensity included statins atorvastatin 10-20 mg daily; fluvastatin, 40 mg twice a day or 80 mg daily; lovastatin, 40 mg daily; pitavastatin, 2-4 mg daily; pravastatin, 40-80 mg daily; rosuvastatin, 5-10 mg daily; and simvastatin, 20-40 mg daily. High-intensity statins included atorvastatin, 40-80 mg daily; and rosuvastatin, 20-40 mg daily.[17] Abnormal lipid values were total cholesterol >200 mg/dL; high-density lipoprotein (HDL) <40 mg/dL; low-density lipoprotein (LDL) >130 mg/dL; and triglycerides (TG) >150 mg/dL.[18] Statin categories were constructed to be unique and not double count individuals.

Upon data acquisition, exclusion of individuals with confounding factors well known to be associated with DED was performed. Individuals were excluded if they used specific medications associated with DED (tricyclic antidepressants, antihistamines, or diuretics); had a history of rheumatoid arthritis, Sjögren's disease, or lupus (ICD-9 and -10 codes 710.0, 710.2, 714.0, M32.x, M35.x, M05.79, M05.89, M06.09, and M06.89), or a history of cataract or refractive surgery (Current Procedural Terminology codes 66984, S0800, and S0810). Odds ratios (ORs) and their associated 95% confidence intervals (CIs) were calculated between DED and each of the above parameters and further stratified by age. All data were analyzed using SAS version 9.4 software (SAS, Cary, North Carolina).

RESULTS

A TOTAL OF 72,931 PATIENTS WERE CONSIDERED FOR INCLUsion in the study. After excluding individuals with the confounding factors identified above, the analyzed cohort consisted of 39,336 individuals, of whom 53.9% were female. Demographic characteristics of the analyzed population are outlined in Table 1. In total, 3,399 patients (8.6%) carried a diagnosis of DED. Low-intensity, moderate-intensity, and high-intensity statin regimens were used by 751 patients (1.9%), 2,655 patients (6.8%), and 1,036 patients (2.6%), respectively. Lipid abnormalities were found in the respective numbers of patients: total cholesterol >200 mg/dL, 4,558 patients (11.6%); HDL <40 mg/dL, 2,078 patients (5.3%); LDL >130 mg/dL, 2,756 patients (7.0%); and TGs >150 mg/dL, 2,881 patients (7.3%).

TABLE 1. Demographics of the Analyzed Study Population

Demographic	Number (%) of Patients (N = 39,336)
Sex	
Males	18,149 (46.1)
Females	21,187 (53.9)
Race	
White	22,701 (57.7)
African American	6,862 (17.4)
Asian	1,194 (3.0)
Native American or Alaskan	177 (0.4)
Other or unknown	8,402 (21.4)
Age groups, y	
18-34	11,259 (28.6)
35-54	10,334 (26.3)
55-64	6,070 (15.4)
≥65	11,673 (29.7)

Table 2 and 3 show the calculated odds ratios and their associated 95% CIs for this cohort. The OR of carrying a diagnosis of DED, given the presence of low-intensity, moderate-intensity, and high-intensity statin use, were 1.39 (95% CI: 1.13-1.72), 1.47 (95% CI: 1.30-1.65), and 1.46 (95% CI: 1.21-1.75), respectively, compared to patients not taking statins. The ORs of carrying a diagnosis of DED, given the presence of total cholesterol >200 mg/dL, HDL <40 mg/dL, LDL >130 mg/dL, and TGs >150 mg/dL were 1.66 (95% CI: 1.52-1.82), 1.45 (95% CI: 1.26-1.67), 1.55 (95% CI: 1.39-1.74), and 1.43 (95% CI: 1.27-1.61), respectively.

DISCUSSION

THIS PAPER REPORTS ANALYSIS OF A LARGE, DIVERSE POPUlation of patients who were analyzed for the association of DED with statin use and dyslipidemia. There was an approximately 40% greater odds of a diagnosis of DED in patients taking statin regimens of all intensities, 60% greater odds for patients with cholesterol >200 mg/dL, and a range of 40% to 50% greater odds with TG >150 mg/dL, HDL <40 mg/dL, or LDL >130 mg/dL. Although previous studies of smaller, select populations support an association between dyslipidemia and MGD or DED, none of those studies have specifically evaluated the association of statin use/intensity and a clinical diagnosis DED.

TABLE 2. Calculated Odds Ratios and Corresponding Confidence Intervals between Statin Therapy and Dry Eye Disease

	Age Groups (y)				
Exposure	18-34	35-54	55-64	≥65	All Ages
Low-intensity statin therapy, OR (CI)	NA[a]	0.85 (0.44-1.62)	1.00 (0.62-1.63)	1.71 (1.33-2.21)	**1.39 (1.13-1.72)**
Moderate-intensity statin therapy, OR (CI)	6.96 (2.63-18.42)	1.13 (0.81-1.58)	1.37 (1.08-1.74)	1.57 (1.35-1.82)	**1.47 (1.30-1.65)**
High-intensity statin therapy, OR (CI)	17.50 (5.99-51.13)	1.15 (0.69-1.90)	1.28 (0.89-1.85)	1.54 (1.21-1.95)	**1.46 (1.21-1.75)**

CI = confidence interval; NA = not applicable; OR = odds ratio.
All Ages values in boldface stands for greater than or equal to 18.
[a]Note: queries for males and females aged 18-34 returned with sample sizes too small to properly calculate odds ratios in that age range.

Previously reported case-control studies support the association of elevated total cholesterol,[9–11] TG,[9–11] and LDL[10,11] with MGD or DED. As well, 1 study found an association of elevated LDL/TG with more severe MGD.[12] However, in those studies, individuals taking lipid-lowering therapy were specifically excluded, limiting this potential confounder but disallowing its evaluation. Another population-based study of 5,627 Korean adults found an association between elevated total cholesterol and LDL with DED in women only.[19] Conflicting results have been found in regard to HDL levels and MGD/DED.[9–11,19,20] In contrast, a population-based study of 3,280 Malay persons in Singapore showed an inverse relationship between LDL and MGD and no significant association with other lipid parameters.[20] A recent analysis of data from subjects in the Blue Mountains Eye Study found no association between hypercholesterolemia and DED; however, oral statin use was associated with moderate to severe DED symptoms based on a questionnaire.[8]

The exact mechanism(s) underlying the relationship between statin use and/or dyslipidemia and MGD/DED are unclear. It is well established that meibomian glands secrete meibum into the tear film, slowing its rate of evaporation.[21–23] Studies have shown that the meibum of individuals with MGD has an increased concentration of cholesterol esters, likely resulting in a higher melting point, increased viscosity, and a propensity toward meibomian gland obstruction.[24,25] While it is plausible that systemic lipid abnormalities may be associated with abnormalities of tear film lipids, no studies have specifically examined this relationship in detail. One study of two subjects failed to identify an association between plasma and tear cholesterol.[26] An alternative hypothetical mechanism relates to the proinflammatory characteristics of LDL[27,28] as inflammation is known to contribute to the pathogenesis of MGD and DED.[6]

Statins exert their effects by inhibition of HMG-CoA reductase, an enzyme which catalyzes the rate-limiting step for the synthesis of sterols and isoprenoids in human meibomian gland epithelial cells.[16,29,30] Thus, it has been postulated that statins may disrupt essential cholesterol synthesis in the meibomian glands.[16] In our study, the risk of DED was similar for low-, moderate-, and high-intensity statin regimens, suggesting that any effect of statin use may not be dose dependent. Alternatively, it is also possible that statin use is only a surrogate marker for treated dyslipidemia and the association of statin use with DED could be spurious. As nearly all patients with dyslipidemia were treated with statins in the present cohort, the effects of statin use and dyslipidemia on the risk of DED could not be separated in this study. Further prospective analyses evaluating the effects of statin use on meibomian gland secretions would provide insights into any influence on meibum quantity and composition in the tear film. Interestingly, topical statin use has been demonstrated to be beneficial in treating dry eye associated with blepharitis.[31,32] The mechanism of this response has not been established, although statins are known to also exert anti-inflammatory effects which could be involved.[31]

To reduce the number of potentially confounding factors, patients with conditions or taking medications that are well known to be associated with DED were excluded. Patients using antihistamines, diuretics, and tricyclic antidepressants were also excluded from analyses because those classes of medications might have been associated with the development or worsening of DED.[33,34] Refractive surgery and cataract surgery can also precipitate or worsen DED.[35–37] Additionally, autoimmune diseases such as lupus, rheumatoid arthritis, and Sjögren's syndrome are strongly associated with DED.[38–40] However, because many other systemic conditions and treatments may have mild potential associations with DED or lipid profiles, there could be other confounding factors that were not controlled for in this study. For example, use of over-the-counter supplements such as omega-3 fatty acids or niacin, which have known effects on serum lipid profiles, were unable to be assessed.

This study possesses several other limitations inherent to retrospective studies, including an inability to establish whether temporal or duration-based associations exist between statin use or dyslipidemia and DED. As well, causes of DED could not be stratified. Because the code for MGD (ICD-10 code H02.88) was not present in ICD-9, its evaluation could not be assessed prior to October 2018 due to not

TABLE 3. Calculated Odds Ratios and Corresponding Confidence Intervals between Specified Serum Lipid Levels and Dry Eye Disease

	Age Groups (y)				
Exposure	18-34	35-54	55-64	≥ 65	All Ages
Elevated total cholesterol, OR (CI)	1.44 (0.82-2.55)	1.38 (1.15-1.66)	1.28 (1.06-1.54)	2.16 (1.89-2.47)	**1.66 (1.52-1.82)**
Low HDL, OR (CI)	1.01 (0.47-2.16)	1.30 (1.00-1.70)	1.62 (1.21-2.15)	1.52 (1.22-1.89)	**1.45 (1.26-1.67)**
High LDL, OR (CI)	1.11 (0.45-2.73)	1.48 (1.18-1.85)	1.18 (0.94-1.48)	1.92 (1.63-2.26)	**1.55 (1.39-1.74)**
Elevated triglycerides, OR (CI)	1.88 (1.08-3.26)	1.41 (1.13-1.76)	1.21 (0.96-1.54)	1.55 (1.31-1.85)	**1.43 (1.27-1.61)**

CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable; OR = odds ratio.
All Ages values in boldface stands for greater than or equal to 18.

having its own code until that point.[41] As such, DED of all potential causes were included. Data from the CDWH database were only available in aggregate, which limited the authors' ability to examine trends in statin use and DED rates based on individualized variables, such as the presence and severity of MGD, tear film breakup time, or Schirmer testing results. The CDWH database does not allow for determination of the exact timing of diagnoses or laboratory values. In addition, the use of diagnostic codes for select patients in the analysis could have introduced classification bias into the study because no specific criteria for the diagnosis of DED could be used. However, previous studies suggest a high degree of consistency between ICD-9 and ICD-10 codes and findings present within medical records.[42,43]

Despite these limitations, this study reports the largest retrospective analysis to date examining DED as associated with statin use and dyslipidemia. This study supports associations among statin use, dyslipidemia, and DED, particularly in elderly patients. Further research is needed to determine any separate effects of dyslipidemia and statin use on DED, to elucidate pathogenic mechanisms involved, and to identify any potential therapeutic targets.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

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