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Dyslipidemia and its association with meibomian gland dysfunction

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Abstract Abnormal serum lipid levels significantly increase the risk for cardiovascular disease. Furthermore, abnormal compositions of cholesterol in glandular secretions have been hypothesized as an etiology for meibomian gland dysfunction, yet this relationship has not been well studied in clinical settings. The primary purpose of this study was to determine if there is an association between dyslipidemia and meibomian gland dysfunction (MGD). The secondary purpose was to identify the factors, if any, that play a role in this association. A case–control study was performed between October 2013 and February 2015 which recruited 109 patients with MGD and 115 control patients without MGD. All participants were of Indian descent and had no history of dyslipidemia. Basic demographic information was collected as well as fasting levels of serum glucose, creatinine, triglycerides, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). To calculate differences between groups, Z test or Student t test were used. A stepwise logistic regression model was used to calculate the estimates of odds ratios (ORs), where MGD was the dependent variable, making the independent variables consist of sex, age, body mass index (BMI), triglycerides $\geq$150 mg/dL, total cholesterol $\geq$200 mg/dL, LDL $\geq$130 mg/dL, or HDL $\leq$40 mg/dL, serum glucose, and serum creatinine. Dyslipidemia, defined by either a fasting total cholesterol level of $\geq$ 200 mg/dL, triglycerides $\geq$150 mg/dL, LDL $\geq$130 mg/dL, or HDL $\leq$40 mg/dL, was detected in 70 cases (64 %) and 21 controls (18 %), $P < 0.001$. Mean levels of triglycerides, total cholesterol, LDL, and HDL were 98.5 $\pm$ 42.1, 203.1 $\pm$ 13.2, 126.1 $\pm$ 10.2, and 53.3 $\pm$ 4.2 mg/dL, respectively, in cases and 82.3 $\pm$ 36.5, 156.6 $\pm$ 14.5, 92.2 $\pm$ 12.4, 45.8 $\pm$ 2.6 mg/dL, respectively, in controls. All differences were statistically significant ($P < 0.05$). MGD was significantly associated with age >65 years (OR 2.1; 95 % CI 1.2–3.2, $P = 0.04$), serum triglyceride concentration $\geq$150 mg/dL (OR 3.2; 95 % CI 1.9–4.4; $P = 0.03$), total cholesterol $\geq$200 mg/dL (OR 14.3; 95 % CI 8.2–20.7, $P < 0.01$), and LDL $\geq$130 mg/dL (OR 9.1; 95 % CI 6.6–13.2, $P < 0.01$). Adults from northern rural India with MGD are more likely to have abnormal serum lipid levels compared to age- and sex-matched adults without MGD. Eye care providers may have a role in discovering undiagnosed dyslipidemia, an important risk factor for cardiovascular illness.

Keywords Meibomian gland dysfunction · Dyslipidemia · Hypercholesterolemia

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Introduction

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 serum cholesterol 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 provide clues 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 $\geq$200 mg/dL, triglycerides $\geq$150 mg/dL, low-density lipoprotein (LDL) $\geq$130 mg/dL, or high-density lipoprotein (HDL) $\leq$40 mg/dL [10–12, 15].

The primary purpose of this study was to determine if there was an association between dyslipidemia and meibomian gland dysfunction (MGD). The secondary purpose of this study was to identify the factors, if any, that play a role in this association.

Methods

This case–control study recruited 109 patients with MGD and 115 control patients without MGD. All participants were of Indian descent, had no history of dyslipidemia, and were enrolled between October 2013 and February 2015. The study was conducted in accord with the Declaration of Helsinki and ethical considerations were approved by the institutional review board at the Krishna Devi (KD) Dalmia Eye Hospital (Rampur, Uttar Pradesh, India).

This study defined MGD by using the International Workshop Group's definition: "a chronic, diffuse abnormality of the meibomian glands, characterized by terminal duct obstruction or qualitative/quantitative changes in the glandular secretion and resulting in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease [16]."

The clinical diagnosis of MGD was based on descriptions of glandular obstruction and meibum quality [17–22]. The evaluation for gland obstruction was obtained by firm digital pressure over the central third of the upper and lower eyelid, while observing the ease of excretion under slit lamp biomicroscopy. The grade assigned for meibomian gland obstruction was based on the system offered by other authors [11, 19–21] as follows: 0 (no obstruction, meibum easily expressed), 1 (mild obstruction, meibum expressible with mild pressure), 2 (moderate obstruction, meibum expressible with moderate pressure), and 3 (complete obstruction, no glands expressible, even with hard pressure). The quality of gland secretion was observed via slit lamp biomicroscopy exam and graded as follows: 0 (clear fluid), 1 (cloudy fluid), 2 (cloudy particulate fluid), and 3 (toothpaste-like). Patients scoring $\geq$2 for either obstruction or meibum quality were considered to have moderate to severe MGD and included in the study.

Exclusion criteria was age <18, a history of hypercholesterolemia, primary or secondary Sjögren syndrome, diabetes, pregnancy, active keratoconjunctivitis, inflammatory or allergic ocular surface diseases unrelated to MGD, corneal arcus, ocular surgery in the past 9 months, lacrimal drainage system dysfunction, or chronic treatment with lipid-lowering drugs, omega-3 fatty acids, beta blockers, or other systemic drugs affecting tearing, as well as the use of topical ophthalmic medications (including corticosteroids) in the 4 weeks before the study.

Controls were recruited from accompanying friends, family, or hospital personnel in order to match the cases by age, gender, and socioeconomic standing. All controls underwent ophthalmic examination and only those without MGD (i.e., grade 0—no gland obstruction, clear expressed meibum) were included. Exclusion criteria for controls were the same as for cases.

Height, weight, body mass index (BMI), total cholesterol, LDL, HDL, triglycerides, fasting serum

glucose, and creatinine levels were obtained from all participants. Dyslipidemia was defined by either a fasting total cholesterol level of ≥200 mg/dL, triglycerides ≥150 mg/dL, LDL ≥130 mg/dL, or HDL ≤40 mg/dL. Abnormalities in fasting serum glucose and serum creatinine were ≥126 and ≥1.4 mg/dL, respectively.

Statistical analysis included comparisons of demographic data to observe differences among cases and controls. Categorical variables were compared by Z test for proportions, and by student t tests for continuous variables. An initial binary logistic regression model, where MGD (yes/no) was considered the dependent variable, provided estimates of odds ratios (ORs). The ORs and 95 % confidence intervals (CIs) were obtained by maximum likelihood estimations and P values <0.05 were considered statistically significant. Independent covariates included in this model were gender, age, BMI, triglycerides ≥150 mg/dL, total cholesterol ≥200 mg/dL, LDL ≥130 mg/dL, or HDL ≤40 mg/dL, glucose, and creatinine (full model). In a separate binary logistic regression model, the dependent variable was dyslipidemia (yes/no). A patient had dyslipidemia if at least one of the following criteria were met: triglycerides ≥150 mg/dL, total cholesterol ≥200 mg/dL, LDL ≥130 mg/dL, or HDL ≤40 mg/dL. Independent covariates included gender, age, BMI, MGD, glucose levels, and creatinine levels (full model). In both regression models, a backward selection technique was used to eliminate covariates which did not contribute significantly to the fit of the model. A significance level of 0.2 or above was used to remove covariates from the multivariable model, and a value of 0.1 or less was used to include variables. All statistical analysis was done with SAS 9.3 (2011 SAS Institute Inc. Cary, NC, USA).

Results

There were no significant differences amongst cases and controls in terms of age, gender, BMI, glucose levels, or serum creatinine levels (Table 1). Patients with MGD had higher mean triglycerides, total cholesterol, LDL, and HDL ($P < 0.05$). The age range among the cases was 20–72 years of age and for the controls it was 19–75 years of age.

As seen in Fig. 1, a higher proportion of patients with MGD had abnormal triglycerides, total cholesterol, and LDL compared to controls ($P < 0.05$), although there was no significant difference in HDL between groups ($P = 0.18$).

In the logistic regression model where MGD was the dependent variable, the only covariates that significantly affected the fit of the model were age, triglycerides, total cholesterol, and LDL levels (Table 2). The Nagelkerke R^2 for this model was 0.68 and revealed that patients ≥65 years old had double the odds of having meibomian gland dysfunction vs. those <65 ($P = 0.04$). Compared to patients with serum triglycerides <150 mg/dL, those with values ≥150 mg/dL had triple the odds of having MGD ($P = 0.03$). A greater disparity was noted for abnormal LDL levels: subjects with serum LDL ≥130 mg/dL had nine times greater odds of having MGD versus those with LDL <130 mg/dL ($P < 0.01$). The largest effect was observed for cholesterol. Individuals with total cholesterol ≥200 mg/dL had nearly a fourteen times higher odds of having MGD vs. those with total cholesterol <200 mg/dL ($P < 0.01$). Again, this logistic regression model did not show a significant association between low levels of HDL and MGD.

In the logistic regression model with dyslipidemia as the dependent variable, the only covariates that significantly affected the fit of the model were gender, age, and MGD (Table 3). The Nagelkerke R^2 for this model was 0.51. This model revealed that men had more than a five times greater odds of having dyslipidemia than women ($P < 0.01$). Subjects ≥65 had more than six times the odds of having dyslipidemia ($P < 0.01$) vs. those <65. Patients with MGD had more than 18 times the odds of having dyslipidemia compared to patients without MGD ($P < 0.01$). This logistic regression model did not show a significant association between BMI and dyslipidemia. Traditionally, R^2 values are reported for linear regression models in order to understand how much of the variance in the model can be explained by the covariates. Although binary logistic regression does not have an exact analogous descriptor such as the R^2 value, during statistical analysis, several pseudo-R^2 values can be generated to approximate the variance in logistic models. Each potential pseudo-R^2 has its limitations, however, the Nagelkerke R^2 was selected

Table 1 Systemic characteristics of patients with meibomian gland dysfunction and controls

	Patients with MGD ($n = 109$)	Controls ($n = 115$)	Cases versus controls
Gender			
Male, *n* (%)	58 (53 %)	60 (52 %)	$P = 0.87$
Female, *n* (%)	51 (47 %)	55 (48 %)	$P = 0.87$
Age in years (mean ± SD)	46.7 ± 9.2	45.9 ± 10.2	$P = 0.51$
	Range (20–72)	Range (19–75)	
BMI (mean ± SD)	22.9 ± 2.8	22.2 ± 2.6	$P = 0.81$
Triglycerides mg/dL (mean ± SD)	98.5 ± 42.1	82.3 ± 36.5	$P = 0.01$
Total Cholesterol, mg/dL (mean ± SD)	203.1 ± 13.2	156.6 ± 14.5	$P < 0.01$
LDL, mg/dL (mean ± SD)	126.1 ± 10.2	92.2 ± 12.4	$P < 0.01$
HDL, mg/dL (mean ± SD)	53.3 ± 4.2	45.8 ± 2.6	$P = 0.03$
Glucose, mg/dL (mean ± SD)	76.3 ± 3.2	74.8 ± 2.9	$P = 0.26$
Creatinine (mean ± SD)	0.92 ± 0.08	0.94 ± 0.07	$P = 0.74$
Prevalence of Dyslipidemia			
Abnormal values for either LDL, HDL, triglycerides, or total cholesterol	70 (64 %)	21 (18 %)	$P < 0.01$

MGD meibomian gland dysfunction represent the cases

BMI body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *MGD* meibomian gland dysfunction. Thresholds for abnormal lipid profile values (Dyslipidemia) were triglycerides ≥150 mg/dL, Total cholesterol ≥ 200 mg/dL, LDL ≥ 130 mg/dL, HDL ≤ 40 mg/dL

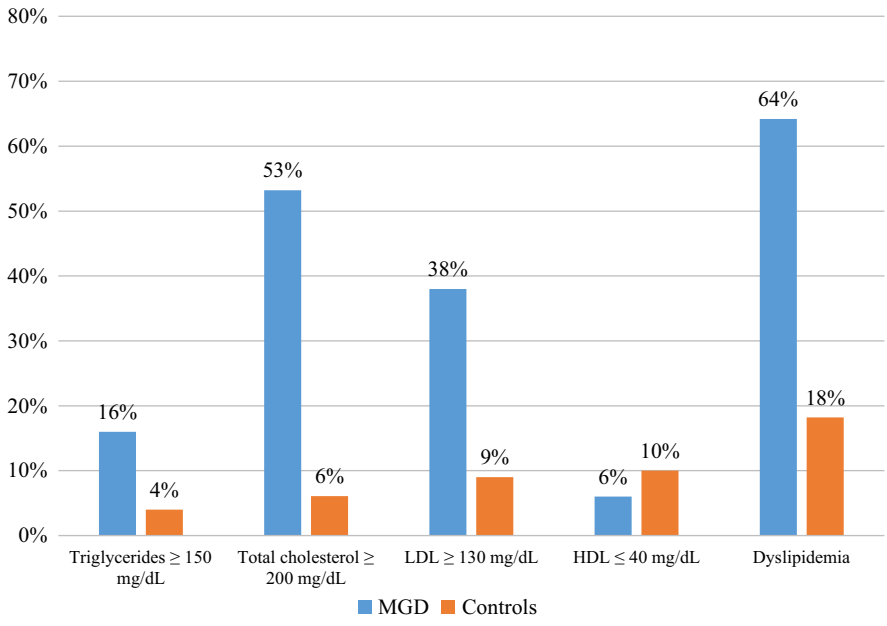

Fig. 1 Prevalaence of abnormal lipid profiles cases vs. controls. *MGD* Meibomian gland dysfunction, represent the cases

MGD = Meibomian Gland Dysfunction, represent the cases.

Table 2 Factors impacting meibomian gland dysfunction in the multivariate logistic regression model

	Odds ratio (95 % CI)	*P* value
Age		
Age < 65 years (Reference)	–	
Age ≥ 65 years	2.1 (1.2–3.2)	0.04
Triglycerides		
Serum concentration < 150 mg/dL (Reference)	–	
Serum concentration ≥ 150 mg/dL	3.2 (1.9–4.4)	0.03
Total cholesterol		
Serum concentration < 200 mg/dL (Reference)	–	
Serum concentration ≥ 200 mg/dL	14.3 (8.2–20.7)	<0.01
Low-density lipoprotein (LDL)		
Serum concentration < 130 mg/dL (Reference)	–	
Serum concentration ≥ 130 mg/dL	9.1 (6.6–13.2)	<0.01

Odds ratios and 95 % confidence intervals for the covariates associated with an increased risk of having meibomian gland dysfunction. Nagelkerke R^2 for this model = 0.68

Table 3 Factors impacting dyslipidemia in the multivariate logistic regression model

	Odds ratio (95 % CI)	*P* value
Gender		
Female (Reference)	–	
Male	5.4 (1.9–8.6)	<0.01
Age		
Age < 65 years (Reference)	–	
Age ≥ 65 years	6.1 (3.8–8.1)	<0.01
Meibomian gland dysfunction		
No MGD (Reference)	–	
MGD	18.2 (13.4–24.6)	<0.01

Odds ratios and 95 % confidence intervals for the covariates associated with an increased risk of having dyslipidemia. Nagelkerke R^2 for this model = 0.51

because it can be scaled from 0 to 1 making it more intuitive for readers [23, 24].

Discussion

Dyslipidemia is a term that represents an abnormal lipid value in one or more of the lipid profiles. Certain forms of dyslipidemia, specifically, low levels of HDL, high levels of LDL, and total cholesterol, have been shown to be independent risk factors for cardiovascular disease [1, 2]. In fact, the US National Institute of Health (NIH) recommends total cholesterol levels stay <200 mg/dL [3]. The European Cholesterol Guidelines Report recommended total cholesterol of <5.0 mmol/L for most people (<193 mg/dL) [25]. However, for patients with cardiovascular disease, the recommendation is lowered to <4.5 mmol/L (<174 mg/dL).

MGD can cause chronic ocular irritation and is not always accurately reported. In mild cases, this condition may not be diagnosed; and as such, some studies postulate a MGD prevalence of 70 % [14, 26]. The cause of MGD is incompletely understood, but changes in meibum composition and/or obstruction of the meibomian glands is thought to be central to the process [27, 28]. Studies show that meibum of MGD patients has different components and proportions of cholesterol compared to the meibum of controls [29]. Specifically, cholesterol esters were always present in the glands of patients with MGD but not necessarily in normal controls [9, 10, 17]. Recent research postulates that increased cholesterol in meibum may play a role in the pathology of MGD [9–12, 29].

Organic substances with a greater number of saturated bonds or larger side chains have higher melting points [30]. This concept can explain why the melting point of normal meibomian secretions ranges from 30 to 34 degrees Celsius while cholesterol, with its numerous structural differences, has a typical melting point of 148 degrees Celsius [27]. Theoretically, meibum with higher concentrations of

cholesterol would have a higher melting point and therefore be more viscous at physiologic temperatures, thus plugging the meibomian glands. This obstruction may alter the tear film's lipid layer, increasing tear evaporation and osmolarity, and in turn leading to the signs and symptoms of evaporative dry eye disease.

Based on the prior body of data which suggested that elevated levels of cholesterol were implicated in MGD, we wanted to assess whether MGD was associated with abnormal levels of total cholesterol and its constituents of LDL, HDL, and triglycerides. Other studies decided to exclude elderly patients on the basis that high age correlates with lipid abnormalities [11, 12]. A study by Villani et al. [31] evaluated age-related changes of the meibomian gland using in vivo laser scanning confocal microscopy. Their work demonstrated that meibomian gland density and diameter significantly decreased with age. Their work underscored not only that there was meibomian gland drop out with age but also revealed histological evidence of age-related atrophy and non-obstructive changes which may be contributory in MGD. Nien et al. [32] aimed to study age-related changes in meibomian glands by using excess human eyelid tissue among patients who underwent canthoplasty. Their samples underwent frozen section and staining. Specific antibodies against peroxisome proliferator-activated receptor γ (PPARγ) were used to identify meibocyte differentiation and Ki67 nuclear antigens were used to identify cycling cells. Their results revealed that aging human meibomian glands undergo decreased meibocyte differentiation and cell cycling that is associated with the development of MGD.

In our study, however, elderly patients were included to bolster the number of participants. Furthermore, if there was a significant effect by age then it could be quantified in our multivariate logistic regression model.

Our exclusion criteria—applied to controls and cases—were designed to limit the confounding effects of either the diagnosis of dry eyes, MGD, or conditions that alter the lipid profile in the patient (i.e., being on lipid-lowering agents). The difficulty of case–control studies is often in the selection of a representative control group. We mitigated a selection bias by choosing controls who were similar to cases in terms of gender, age, and especially socioeconomic standing—which is believed to reflect greater similarity in dietary intake and overall health [33, 34].

Our study found that patients with MGD have significantly higher mean values for triglycerides, total cholesterol, LDL, and HDL versus individuals of a similar age, gender, and BMI without MGD ($P < 0.05$). The greatest variation was observed in LDL and total cholesterol levels, where the absolute differences in mean values were 34.4 and 46.5 mg/dL, respectively. The differences observed in this study lend credibility to the theory that higher levels of serum cholesterol values are related to meibomian gland dysfunction.

Aside from having higher mean lipid profile values, patients with MGD have a disproportionately higher representation amongst those classified as having dyslipidemia (Fig. 1). Patients with MGD more often had serum triglycerides ≥150 mg/dL, total cholesterol ≥200 mg/dL, and an LDL ≥130 mg/dL. However, when considering patients with serum HDL ≤40 mg/dL there was no significant difference between those with or without MGD. Given the high prevalence of dyslipidemia among patients with MGD it appears that many patients were unaware that they had abnormal lipid values. This fits with prior notions that apparently healthy patients, particularly in rural India where routine health screening is underutilized [35, 36], do not seek annual physician examinations. This behavior is particularly relevant in economies where preventative medicine is under prioritized [37, 38].

According to our first logistic regression model (Table 2), an age >65 mildly increased the odds of having MGD, however, the larger factors were abnormally high serum triglycerides, LDL, and total cholesterol which increased the odds of having MGD by a factor of roughly 3, 9, and 14, respectively.

According to our second logistic regression model (Table 3), being a male and being elderly moderately increases the odds of having dyslipidemia, yet the largest effect in this model was played by the presence of MGD (OR 18.2, 95 % CI 13.4–24.6, $P < 0.01$). The results from both regression models depict a robust association between dyslipidemia and MGD—supporting the notion that abnormal cholesterol levels, especially serum LDL ≥130 mg/dL and serum total cholesterol ≥200 mg/dL, are associated with altered meibum composition that can be detected in slit lamp biomicroscopy of patients with moderate to severe MGD. Conversely, for patients in whom a diagnosis of dyslipidemia is unknown or was previously absent, the

presence of moderate to severe MGD may suggest an association with underlying serum lipid abnormalities.

The implications of this study are two-fold. Firstly, eye care specialists may have an increasing role in the detection of dyslipidemia, a known risk factor for cardiovascular disease [1, 6, 7]. Secondly, if prospective studies are able to demonstrate a causal relationship between dyslipidemia and MGD, it may lead clinicians to consider oral lipid-lowering medications for the treatment of meibomian gland dysfunction.

Similar as well as dissimilar results can be found in recent studies. Bukhari et al. [12] performed a study in Saudi Arabia involving 132 subjects with MGD and 104 without MGD. The aim of this study was to observe a correlation between serum fasting lipids and MGD severity. This author concluded that the presence of MGD did not have a correlation with the presence or absence of dyslipidemia. However, in patients with MGD, as the severity of disease increased, so did the proportion with elevated levels of triglycerides and LDL. Bukhari suggests that in patients with MGD, one way to monitor progression would be to observe fasting serum lipid levels. A case–control study by Pinna et al. [11], in Italy, aimed to investigate a correlation between MGD and hypercholesterolemia (total cholesterol $\geq$200 mg/dL) in patients aged 18–54 years. Their results, like ours, showed that mean levels of triglycerides, total cholesterol, LDL, and HDL were higher in patients with MGD compared to those without MGD. Further, their results showed that MGD was associated with hypercholesterolemia (total cholesterol $\geq$200 mg/dL) with an OR of 28 (95 % CI 7.88–99.5, $P < 0.01$).

Our study is limited by the fact that a case–control study cannot determine cause and effect. A prospective study is needed to show that abnormal serum cholesterol levels cause MGD. Second, the precise etiology behind MGD is unknown and postulated to be multifactorial. The implication of abnormal serum cholesterol levels being related to the pathogenesis of MGD is still a nascent theory in this field. Third, the generalizability of this study is limited by the homogenous sample (all patients were of Indian descent). Genetic characteristics and dietary regional practices have already been shown to alter an individual's lipid profile [39], which may obfuscate the recommendations of this study. Lastly, our decision to include patients older than the age of 65 was intentional, even though we understand that age is a potential confounder for dyslipidemia and that other authors excluded elderly patients [11] for this reason. However, our multivariate regression models demonstrated that although the effect of age may have been significant, it did not have the largest effect compared to other covariates in the model.

In conclusion, our results suggest that patients with moderate to severe MGD have greater abnormalities in their serum lipid profiles than individuals without MGD. Clinicians in other regions are encouraged to perform similar studies to learn if such relationships exist. Pending confirmatory results in larger studies, MGD may become a sign of undiagnosed dyslipidemia and the eye care provider may have a role in the early diagnosis of an important risk factor for cardiovascular disease.

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Compliance with ethical standards

Conflict of interest None of the authors have any proprietary interests or conflicts of interest related to this submission.

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