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High Total Cholesterol Levels And Its Relation With Ocular Tear Film Instability

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Abstract:

The stability of the tear film is essential for a healthy visual system. Tear film instability could result in dysfunction of the conjunctiva and eyelids, a reduction in corneal transparency which produce several vision problems where dry eye syndrome is most common. The current case-control study was undertaken to determine relationship between serum cholesterol level and ocular tear film instability in general population of Nepal.This study was conducted on 20 hypercholesterolemic (case) and 20 age and sex matched control (normocholesterolemic) participants. In order to assess tear film instability, the Ocular Surface Disease Index (OSDI); Inter-blink interval (IBI) and Tear-film breakup time (TBUT) was evaluated. OSDI score was significantly higher ($p<0.001$) in the hypercholesterolemic participants than that of normocholesterolemic participants. However; TBUT and IBI were significantly lower in the hypercholesterolemic participants than that of control participants. This study showed that serum cholesterol profile parameters were significantly and positively correlated with Ocular Surface Disease Index score and negatively and significantly correlated with inter-blink interval and tear-film breakup time. This study also showed that total cholesterol, LDL and triglyceride had highest predictability of ocular tear film instability. The hypercholesterolemia may be induces pathological changes in the ocular surface including the conjunctival and corneal epithelia, and meibomian gland could contribute to abnormal meibum and unstable tear film overlying the ocular surface resulted in the occurrence of DED.

Keywords: Hypercholesterolemia; Ocular tear film instability; Dry eye disease

Introduction:

Tear film is an important thin layer that covers the cornea and conjunctiva (Bron et al. 2004, Chun et al. 2013; Alanazi 2019a). It is flow over the ocular surface and provide oxygen, nutrition to the corneal surface and wash debris away, regulate osmotic pressure and acts as a barrier against microorganism infections (Georgiev et al. 2017, Alanazi 2019b). Ocular health is largely dependent on the tear film, as it safeguards a

smooth, perfect, and regular ocular surface by keeping the conjunctiva lubricated and moistened protecting the ocular surface. Lipids are important components of the tear film, which keeps the ocular surface smooth and precludes hasty evaporation of tears from the ocular surface (Bron et al. 2004; Rathna kumar et al. 2018).The meibomian glands which are tubulo-acinar holocrine glands are mainly release lipid of tear film layer during their secretion process of entire contents(Butovich 2011). The secretion of meibomian gland is normally lipid in nature which containing a mixture of non-polar wax and sterol esters,phospholipids, glycolipids, and triglycerides (Nicolaides et al. 1981; Rathna kumar et al. 2018).

However, in reality the structure and function of the tear film is very complex. The stability of the tear film is essential for a healthy visual system. Tear film instability could result in dysfunction of the conjunctiva and eyelids, a reduction in corneal transparency which produce several vision problems where dry eye syndrome is most common (Alanazi 2019b).Dry eye disease (DED) is a chronic, multi-factorial ocular surface disease that negatively affects a significant number of individuals worldwide (Wang et al. 2023). It is characterised by inflammation of the ocular surface and reduction in tear production, therefore ultimately loss of homeostasis of the tear-film to lubricate ocular surface. Its prevalence can vary widely across worldwide even within the country due to variation of geography and climate. Its prevalence increasing continuously through worldwide from 7% to around 33% and it has been identified as a serious public health problem and produced a substantial burden on health sectors (Miljanovic et al. 2007; Tong et al. 2010; Wang et al. 2023).There are multiple causative factors such as air pollution, high temperature, exposure of sunlight, low humidity, exposure to toxic agents, airborne particles, smoking, and drugsassociated with dry eye.

A series of epidemiologic studies have firmly established abnormal lipid levels are one of the important risk factors for cardiovascular disease and stroke, the leading causes of worldwide mortality (Muntner et al. 2014; Braich et al. 2015; Mok and Kim 2015; Larsson et al. 2015). Studies have shown a link between increased cholesterol and meibomian gland dysfunction (Dao et al. 2010; Pinna et al. 2013; Bukhari 2013; Braich et al. 2015; Alanazi 2019b). Several studies documented abnormal serum cholesterol levels in meibomian gland dysfunction patients (Dao et al. 2010; Pinna et al. 2013; Bukhari 2013). Meibomian gland dysfunctioncould result in tear film instability which produce several vision problems such as dry eye syndrome is most common.

However, epidemiological study on relation of increased cholesterol level and ocular tear film instability in general population of Nepal is scanty. Therefore, this hospital-based case-control study was undertaken to determine relationship of serum cholesterol level and ocular tear film instability in general population of Nepal.

Methods and Materials:

This hospital-based case-control study was conducted on patients with hypercholesterolemia presenting to the outpatient department of ophthalmology, National Medical College, Birgunj, Nepal from March 2023 to February 2024. National Medical College in Birgunj is located 275 km from Kathmandu, the capital of Nepal. The hospital has eye department which serves local peoples residing in southern region of Nepal. This study randomly included 20 adult male patients aged 19 to 40 years with hypercholesterolemia during the study period. Patients with history of ocular surgery, diabetes, anemia, vitamin A and D deficiency, thyroid disorder, smokers, contact lens wearer, and individual with a high BMI were excluded from this study. Subjects older than 40 years were also excluded from the study since risk factor of dry eyes is aging too. In addition of hypercholesterolemia patients, an aged match control group consisting of 20 male subjects with normal cholesterol level was recruited. The study protocol was approved by the Institutional Review Board of National Medical College, Birgunj. The purpose and protocol of the study was explained to each eligible patient and written consent was obtained from the study participants.

12 h fasting blood sample was drawn from each participants to estimate blood cholesterol level. Total cholesterol, low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) and triglycerides were analyzed by using commercial cholesterol quantitation assay kits. The Plasma cholesterol more than 200 mg/dl included as hypercholesterolemia (Costa et al. 2003).In order to assess ocular dry eye disease, the Ocular

Surface Disease Index (OSDI) questionnaire was applied on both case and control participants. The OSDI questionnaire has12-item related to dry eye symptoms. It has three subscales: ocular symptoms, vision-related function, and environmental triggers. Final score of OSDI is ranged from 0 to 100 with scores 0 to 12 denote normal, 13 to 22 denote mild dry eye disease, 23 to 32 denote moderate dry eye disease, and >33 denote severe dry eye disease (Grubbs et al. 2014). Blinks were captured over 10 minutes for 10 normal and 10 dry eye subjects while viewing a standardized televised documentary. Fifty five blinks were analysed for each of the 20 subjects.The inter-blink interval (IBI) and tear-film breakup time (TBUT) was evaluated by using slit lamp and fluorescein strip following standard procedure and guideline (Methodologies to diagnose and monitor dry eye disease 2007). The tear-film breakup time less than 10 sec considered dry eye diseases (Dogru et al. 2016.)

The categorical variables were summarized by frequency and percentage and quantitative variables were summarized by their mean and standard deviation respectively. The Student's t test was used to assess difference in quantitative variables and Chi-square test was used for categorical variables. Correlation analysis was done to assess the relationship between the blood cholesterol level and ocular tear film instability parameters. The data was analysed by using SPSS software version 20.0 (SPSS Inc., Chicago, Illinois, USA) and p-value <0.05 was considered as level of significance.

Results:

The physical characteristics of the hypercholesterolemic (case) and control (normocholesterolemic) participants were presented in the Table 1.

Table 1: Physical characteristics, serum lipid profile levels and ocular tear film instability parameters of the case group and control group participants

	Case Group	Control Group	t (*p*)
Age (year)	28.95±5.79	28.70±7.06	0.122 (NS)
Height (cm)	162.89±5.35	163.73±4.60	0.529 (NS)
Weight (Kg)	59.14±8.89	52.31±8.19	2.527 (0.01)
BMI (kg/m^2)	22.23±2.75	19.47±2.58	3.278 (0.01)
Total cholesterol (mg/dl)	234.38±18.83	149.53±26.65	11.63 (0.001)
HDL (mg/dl)	71.46±10.77	45.34±8.82	8.392 (0.001)
LDL(mg/dl)	160.52±23.64	69.94±13.27	14.941 (0.001)
VLDL(mg/dl)	56.96±10.72	31.45±6.26	9.187 (0.001)
Triglyceride (mg/dl)	317.97±57.58	156.63±25.99	11.421 (0.001)
OSDI	14.7±7.47	7.85±3.08	3.791 (0.001)
TBUT (Sec)	12.55±7.55	25.15±8.84	4.847 (0.001)
IBI (Sec)	3.65±1.76	5.85±1.66	4.069 (0.001)

OSDI-Ocular Surface Disease Index; IBI-inter-blink interval; TBUT-and tear-film breakup time; LDL-low density lipoprotein; HDL-high density lipoprotein; VHDL-very high density lipoprotein

The average age of case and control participants was 28.95±5.79 years and 28.70±7.06 years respectively and they were not significantly differing. The average BMI of case participants (22.23±2.75 kg/m^2) was significantly higher ($p<0.01$) than that of control participants (19.47±2.58 kg/m^2). However; the average BMI value of both case and control participants was with in normal range. Total cholesterol level of case and control participants was 234.38±18.83 mg/dl and 149.53±26.65mg/dl respectively. In order to assess the ocular tear film instability, OSDI, TBUT and IBI were studied and those were 14.7±7.47; 12.55±7.55 sec and 3.65±1.76 sec respectively for hypercholesterolemic participants and 7.85±3.08; 25.15±8.84 sec and

5.85±1.66 sec for normocholesterolemic participants respectively in Table 2. OSDI score was significantly higher ($p<0.001$) in the hypercholesterolemic participants than that of normocholesterolemic participants. However; TBUT and IBI were significantly lower ($p<0.001$) in the hypercholesterolemic participants than that of normocholesterolemic participants.

Table 2: Correlation matrix of BMI and serum lipid profile levels with ocular tear film instability parameters

	BMI	Total cholesterol	HDL	LDL	VLDL	Triglyceride	OSDI	TBUT	IBI
BMI	1	0.513***	0.375*	0.545***	0.406**	0.437**	0.534***	-0.388*	-0.519**
Total cholesterol	0.513***	1	0.718***	0.885***	0.677***	0.867***	0.671***	-0.804***	-0.690***
HDL	0.375*	0.718***	1	0.791***	0.576***	0.783***	0.413**	-0.451**	-0.379*
LDL	0.545***	0.885***	0.791***	1	0.771***	0.871***	0.658***	-0.646***	-0.629***
VLDL	0.406**	0.677***	0.576***	0.771***	1	0.654***	0.457**	-0.515***	-0.541***
Triglyceride	0.437**	0.867***	0.783***	0.871***	0.654***	1	0.603***	-0.692***	-0.608***
OSDI	0.534***	0.671***	0.413**	0.658***	0.457**	0.603***	1	-0.758***	-0.755***
TBUT	-0.388*	-0.804***	-0.451**	-0.646***	-0.515***	-0.692***	-0.758***	1	0.814***
IBI	-0.519**	-0.690***	-0.379*	-0.629***	-0.541***	-0.608***	-0.755***	0.814***	1

*p<0.05; **p<0.01; ***p<0.001

Correlation analysis revealed that all the serum cholesterol profile parameters were significantly and positively correlated with OSDI score. Whereas; TBUT and IBI were significantly and negatively correlated with the cholesterol profile parameters (Table 2). Similarly; participants BMI has positive and significant correlation with OSDI and negative correlation with TBUT and IBI. Among the predictable variables in the present study, total cholesterol, LDL and triglyceride had highest predictability of ocular tear film instability (Fig: 1; 2 and 3).

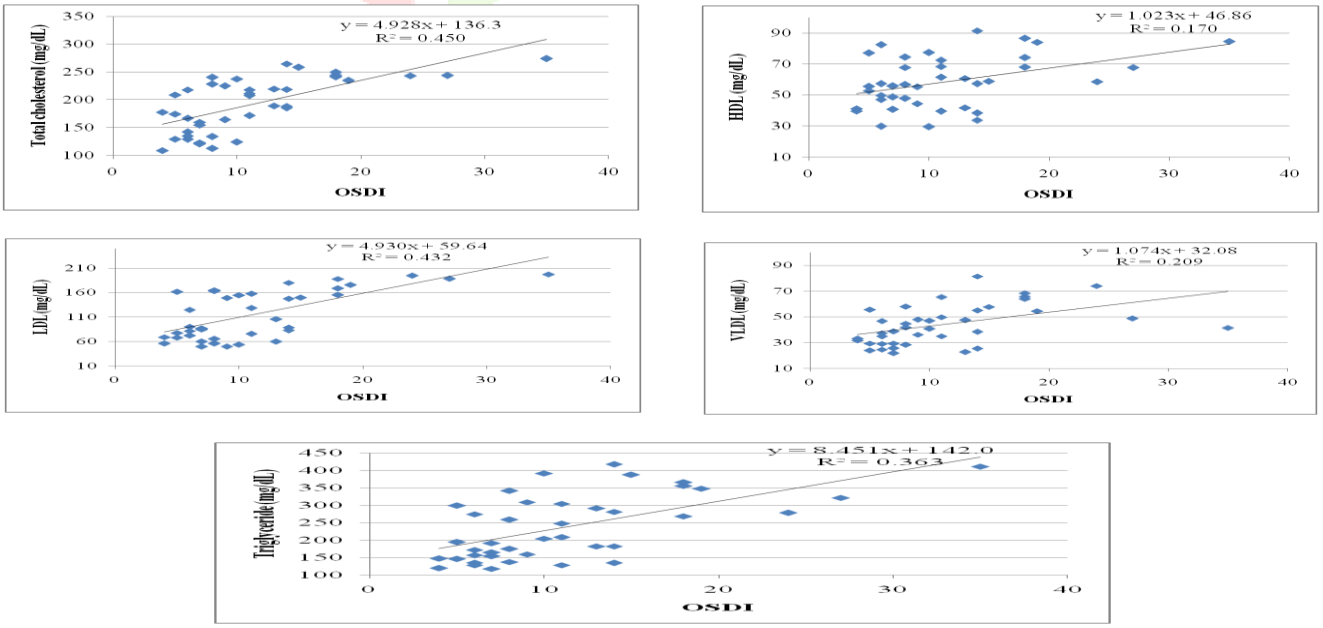

Figure 1: Scatter plot of Ocular Surface Disease Index (OSDI) with serum lipid profile parameters

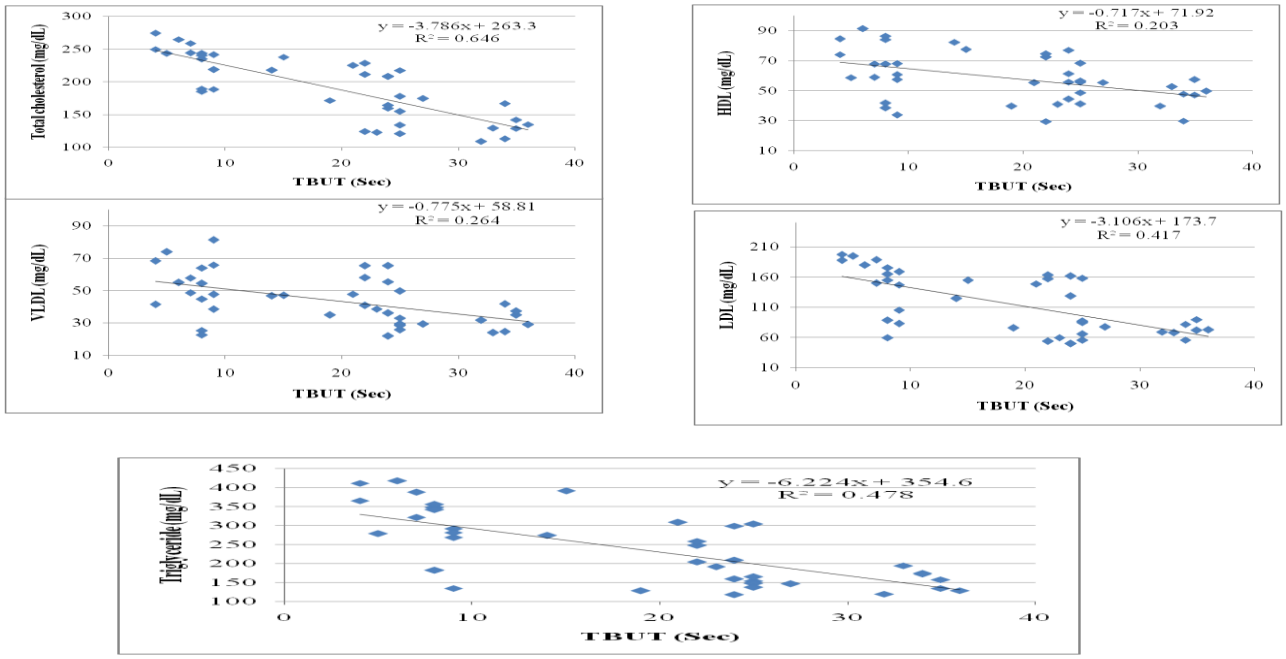

Figure 2: Scatter plot of Tear-film breakup time (TBUT) with serum lipid profile parameters

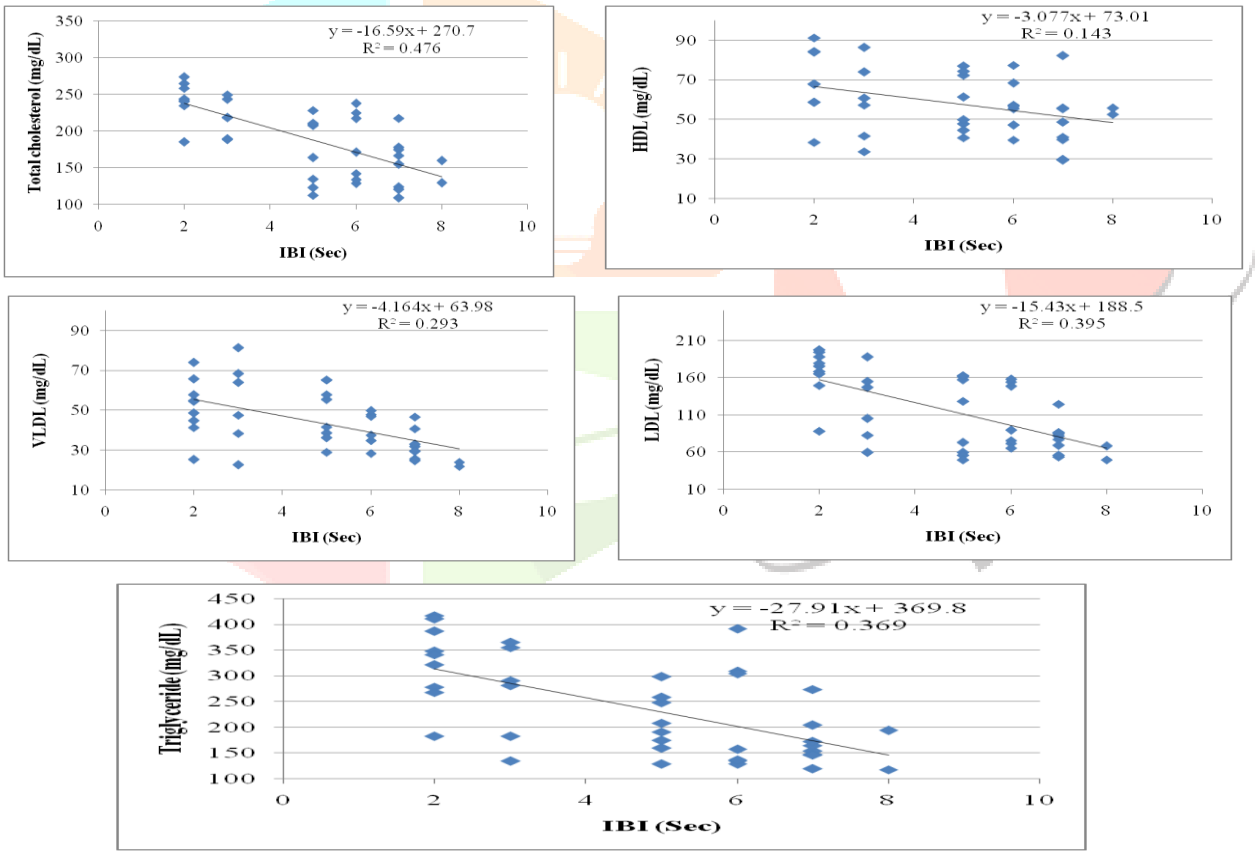

Figure 3: Scatter plot of Inter-blink interval (IBI) with serum lipid profile parameters

Discussion:

Globally, dry eye disease (DED) is a common multifactorial ocular surface disease and the major cause of ophthalmology clinics visit (Wang et al. 2023; Li et al. 2023). The patients with DED, inflammation and reduction in tear production causes homeostasis of the tear-film becomes out of balance, and producesymptoms such as dryness, itching, irritation, fatigue and blurred vision. Thereforeunderstanding of the causativefactors for DED may raise public awareness and improve ophthalmologists' management for

these patients. There are well-recognised multiple causative factors include advanced age, female sex, Asian ethnicity, air pollution, high temperature, high altitude, exposure of sunlight, low humidity, exposure to toxic agents, airborne particles, smoking, computer usage, contact lens wear, systemic medications, ocular surgery, glaucoma, autoimmune diseases, metabolic disorders associated with dry eye disease (Craig et al. 2017; Li et al. 2023).

Dyslipidaemia implies abnormalities in serum lipid levels, including elevated total cholesterol, LDL and triglycerides and decreased HDL. Series of epidemiologic studies have established dyslipidaemia are one of the important causative factor of multi-organ dysfunction and the leading causes of cardiovascular disease and stroke and continues to be a significant public health distress worldwide (Muntner et al. 2014; Braich et al. 2015; Mok and Kim 2015; Larsson et al. 2015). Over the past few years, epidemiological analyses have shown a link between dyslipidaemiaand ophthalmic disorders such as diabetic retinopathy, meibomian gland dysfunctionassociated DED (Dao et al. 2010; Pinna et al. 2013; Bukhari 2013; Braich et al. 2015; Alanazi 2019b). The present study also revealed that serum cholesterol profile parameters were significantly associated with ocular tear film instability parameters. This study showed that serum cholesterol profile parameters were significantly and positively correlated with Ocular Surface Disease Index score and negatively and significantly correlated with inter-blink interval and tear-film breakup time. This study also showed that total cholesterol, LDL and triglyceride had highest predictability of ocular tear film instability.Several epidemiologic studies have showed the association between dyslipidaemia andmeibomian gland dysfunction; which is the main cause ofloss of homeostasis of the tear-film (Dao et al. 2010; Pinna et al. 2013; Bukhari 2013; Braich et al. 2015; Alanazi 2019b; Wang et al. 2023; Li et al. 2023). The mechanisms of dyslipidaemia mediated tear-film instability and development of DED remain elusive. One possible explanation is that hypercholesterolemia potentially induces pathological changes in the ocular surface including the conjunctival and corneal epithelia, and meibomian gland. These ocular surface epithelia inflammatory changes could contribute to abnormal meibum and unstable tear film overlying the ocular surface resulted in the occurrence of DED (Bu et al. 2019; Li et al. 2023).Wu et al. (2020) and Bu et al. (2021) stated that a continuous high-fat diet was found to be decrease of tear secretion and reduce lipid accumulation via the activation of inflammation and oxidative stress of the ocular surface.Yagyu et al. (2020) reported that by knocking out cholesterol acyltransferase, an important enzyme catalysing the esterification of cholesterol, the experimental animal developed dry eye-related ocular surface changes due to atrophy of the meibomian glands.

Conclusion:

The hypercholesterolemic participants have significantly higher OSDI score than that of normocholesterolemic participants. However; TBUT andIBI were significantly lower in the hypercholesterolemic participants than that of control participants. Serum cholesterol profile parameters were significantly and positively correlated with Ocular Surface Disease Index score and negatively and significantly correlated withinter-blink interval and tear-film breakup time. Total cholesterol, LDL and triglyceride had highest predictability of ocular tear film instability. The hypercholesterolemia may be induces pathological changes in the ocular surface including the conjunctival and corneal epithelia, and meibomian gland could

contribute to abnormal meibum and unstable tear film overlying the ocular surface resulted in the occurrence of DED.

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