Original Article

Association of Keratoconus with Elevated Serum Low-Density Lipoprotein (LDL): A Cross-Sectional Comparative Study

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Abstract

Background: Keratoconus (KC/KCN) is a progressive corneal ectasia traditionally considered a localized biomechanical disorder; however, emerging evidence highlights the role of systemic metabolic factors and oxidative stress in its pathogenesis.

Objective: This study aims to evaluate the association between serum low-density lipoprotein (LDL) levels and progressive keratoconus in a Bangladeshi cohort.

Methods: This case-control study was conducted from July 2024 to June 2025 at Vision Eye Institute and Hospital, Dhaka. It included 47 patients with progressive keratoconus and 48 age- and gender-matched controls with refractive errors but no keratoconus. Progression was defined as >1.00 D(Diopter) increase in K-max (Meximum keratometry) over one year with minimum pachymetry ≥400 µm. Exclusion criteria eliminated confounding systemic and ocular conditions. Fasting lipid profile, blood glucose, BMI, keratometry, and pachymetry were assessed. Statistical analysis was performed using SPSS, with $p < 0.05$ considered significant.

Results: No significant differences were found in age ($p = 0.29$), gender ($p = 0.47$), BMI ($p = 0.62$), or fasting glucose ($p = 0.68$) between groups. Total cholesterol, triglycerides, and HDL were also comparable. However, mean LDL was significantly higher in keratoconus patients (112.86 ± 36.34 mg/dL) compared to controls (97.78 ± 31.89 mg/dL, $p = 0.03$). Corneal parameters differed significantly, with higher K-max (57.41 ± 5.17 D vs. 46.19 ± 3.61 D, $p < 0.01$) and lower pachymetry (481.32 ± 56.33 µm vs. 532.59 ± 42.37 µm, $p < 0.01$).

Conclusion: Elevated serum LDL is significantly associated with keratoconus, suggesting a potential role of systemic metabolic factors and oxidative stress in its pathogenesis. Monitoring dyslipidemia may aid in risk stratification and management, warranting further research.

Keywords: Keratoconus; LDL; Dyslipidemia; Corneal Ectasia; Oxidative Stress; Bangladesh.

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Introduction

Keratoconus is a progressive, non-inflammatory corneal ectatic disorder characterized by corneal thinning and protrusion, leading to irregular astigmatism, myopia, and ultimately vision impairment.[1] This condition typically manifests in adolescence or early adulthood and progresses over several years, necessitating careful monitoring and intervention to prevent severe visual compromise.[2] While traditionally considered a biomechanical disorder, emerging evidence highlights the intricate interplay of genetic predispositions and environmental factors, including oxidative stress and inflammatory processes, in its pathogenesis.[3,4] Specifically, heightened levels of inflammatory markers, including proteases, cytokines, and tumor necrosis factor-alpha, have been detected in the tear film of keratoconus patients, indicating a localized inflammatory response. Systemic inflammatory markers, such as the monocyte-to-HDL-cholesterol ratio and neutrophil-to-lymphocyte ratio, have also been found to be elevated in individuals with keratoconus, suggesting a broader systemic involvement.[5·] Furthermore, studies have linked increased systemic oxidative stress to keratoconus, indicating that an imbalance between pro-oxidants and antioxidants may contribute to disease progression.[4] Given these systemic associations, recent investigations have also begun to explore the potential role of metabolic markers, such as lipid profiles, in the pathophysiology of keratoconus, noting a possible link between dyslipidemia and disease presentation.[2] A pilot molecular study has revealed distinctions in metabolic pathways concerning energy production, lipid metabolism, and amino acid metabolism between keratoconus and normal corneas, further supporting the need for a comprehensive assessment of lipid profiles in affected individuals. This cross-sectional comparative study was therefore undertaken to investigate the association between keratoconus and serum lipid levels, particularly low-density lipoprotein, aiming to contribute to a deeper understanding of potential systemic metabolic risk factors for this ocular condition. This investigation aims to determine if elevated serum LDL levels are significantly associated with the presence of keratoconus, thereby elucidating a potential systemic metabolic component in its etiology. This study hypothesizes that individuals with keratoconus will exhibit significantly higher levels of serum low-density lipoprotein compared to age and gender-matched controls (Non-Keratoconus patients). Understanding such associations could inform new diagnostic markers and potential therapeutic strategies targeting systemic metabolic pathways to mitigate disease progression.

Materials and Methods

This cross-sectional comparative study conducted in Vision Eye Institute and Hospital, Dhaka, Bangladesh from July 2024 to June 2025 which included 47 patients diagnosed with keratoconus Who had history of progression and 48 age and gender matched normal individual with only refractive error and no sign of keratoconus or any other ocular disease were taken as control (Non-Keratoconus patients) by purposive sampling.

Progression of keratoconus was considered as an increase of 1.00 diopter or more in K-max over a one-year period prior to the inclusion in the study, alongside a minimum corneal pachymetry of 400 microns at the thinnest point. Diagnosis of keratoconus was established by a corneal specialist based on characteristic slit lamp biomicroscopy findings of localized corneal thinning and ectasia, further corroborated by Pentacam examinations to record flat, steep, and maximum simulated keratometric readings, as well as corneal pachymetry.[6,7,8]

The primary outcome of the study was the difference in fasting serum LDL levels between keratoconus and control (Non-Keratoconus patients) groups. A sample size calculation was performed based on detecting a moderate standardized effect size (Cohen's $d \approx 0.44$), corresponding to an anticipated mean LDL difference of approximately 15 mg/dL with a pooled standard deviation of approximately 34 mg/dL.

Assuming a two-sided alpha of 0.05, 1:1 allocation ratio, and 80% statistical power, the required sample size was estimated to be approximately 82 participants per group (164 total). Due to feasibility constraints and the defined study period, 47 keratoconus patients and 48 controls were enrolled. Based on the observed effect size and sample, the achieved post-hoc power for detecting the LDL difference was approximately 57%. Therefore, the study should be interpreted as exploratory in nature, particularly for secondary lipid outcomes.

Any existing causes of dyslipidaemia, including poor dietary habits, physical inactivity, smoking, hypothyroidism, and diabetes, were systematically excluded from this study through comprehensive patient history collection, thorough clinical examinations, and analysis of both previous and current laboratory blood test results.

Morning fasting flood samples were subsequently collected to assess fasting serum lipid profiles, which encompassed Total Cholesterol, triglyceride, LDL, and HDL levels, alongside a measurement of Fasting Blood Sugar (FBS). Demographic information, including age, sex, education level, height (cm), and weight (kg), was meticulously recorded for all participants.

Height and weight measurements were obtained using a digital height and meter measurement device, and the Body Mass Index was calculated for each participant using the standard formula: BMI = Weight (kg) / height^2 (m^2). BMI categories were subsequently defined as lean (< 25 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥ 30 kg/m^2), with a specific focus on the ≥ 30 kg/m^2 threshold for defining high BMI in the current analysis. Additionally, maximum keratometry and central corneal pachymetry were measured for all participants, allowing for a comparative analysis of these key corneal parameters between the keratoconus and control groups.[2]

The inclusion criteria for the study comprised patients with progressive keratoconus and age-matched controls (Non-Keratoconus patients) exhibiting normal corneal topography, with specific exclusion criteria encompassing prior ocular surgeries, corneal trauma, active systemic or ocular inflammation, and certain systemic diseases that could confound the results.[6,7] Exclusion criteria were stringently applied to ensure the homogeneity of the study population, encompassing individuals with a history of keratorefractive surgery, ocular surgery, corneal cross-linking, or corneal rings implantation, as well as those with severe dry eye, pregnancy, previous corneal scar or hydrops, and other ocular diseases apart from keratoconus.[9] Patients with a history of diabetes, those who had undergone eye surgery, or who had uveitis, glaucoma, or dry eye disease were also excluded.[10]

All statistical analyses were performed using SPSS software, with quantitative data compared between groups using Student's t-test or Mann-Whitney U test, as appropriate for normality.[5] Categorical data were analyzed using chi-square tests or Fisher's exact tests, and a p-value less than 0.05 was considered statistically significant for all analyses.[11]

The ethical approval for this study was obtained from the Institutional Review Board of Vision Eye Institute and Hospital, ensuring compliance with the Declaration of Helsinki.[12] All participants provided written informed consent before their inclusion in the study, or informed consent was obtained from a legal guardian for participants under 18 years of age.[13]

Results

This section presents the findings from the comparative analysis between the keratoconus and control groups, detailing demographic characteristics, lipid profiles, and corneal parameters.

Table 1: Demographic Characteristics of Study Participants

Variables	Keratoconus patients (n=47)	Non-keratoconus patients (n=48	P value
Gender			
Male	26 (55.32%)	23 (47.92%)	0.47
Female	21 (44.68%)	25 (52.08)	
Age Group (years)			
0-10 Yrs.	3 (6.38%)	1 (2.08%)	0.29
11–20 Yrs.	19 (40.43%)	17 (35.42%)	
21–30 Yrs.	24 (51.06%)	23 (47.92%)	
31–40 Yrs.	1 (2.13%)	7 (14.58%)	
Total	47 (100%)	48 (100%)	
Mean age ± SD	22.71±11.84	25.51±13.47	

SD = standard deviation

Table 1 summarizes the demographic features of the study participants, highlighting the distributions of gender and age groups within both the keratoconus and non-keratoconus cohorts. The mean age of the participants in the keratoconus group was 22.71 ± 11.84 years, while in the control group it was 25.51 ± 13.47 years, with a p-value of 0.29, indicating no statistically significant difference in age between the two groups. In terms of gender, the keratoconus group comprised 26 males (55.32%) and 21 females (44.68%), compared to the non-keratoconus group with 23 males (47.92%) and 25 females (52.08%). The p-value for gender distribution was 0.47, confirming no statistically significant difference. This demographic parity in age and gender between the cohorts ensures that any observed differences in lipid profiles or corneal parameters can be more confidently attributed to the presence of keratoconus rather than confounding demographic factors.[14, 15]

Table 2: Clinical Distribution of Characteristics in Patients with and Without Keratoconus

Parameters	Keratoconus patients (n=47)	Non-keratoconus patients (n=48)	Mean Difference (95% CI)	Cohen's d	P-value
BMI (kg/m^2)	23.69±5.35	24.21±4.97	-0.52 (-2.60 to 1.56)	-0.10	0.62
FBS level (mmol/L)	4.71±2.19	4.92±2.75	-0.21 (-1.22 to 0.80)	-0.08	0.68
Total cholesterol (mg/dl)	204.76±62.59	178.38±76.33	26.38 (-2.06 to 54.82)	0.38	0.07
Triglyceride (mg/dl)	136.58±79.12	118.93±71.48	17.65 (-13.80 to 49.10)	0.23	0.26
LDL (mg/dl)	112.86±36.34	97.78±31.89	15.08 (1.16 to 29.00)	0.44	0.03
HDL (mg/dl)	36.17±16.62	41.31±18.11	-5.14 (-12.19 to 1.91)	-0.30	0.09
K-max (D)	57.41±5.17	46.19±3.61	11.22 (9.39 to 13.05)	2.50	<0.01
Pachymetry (μm)	481.32±56.33	532.59±42.37	-51.27 (-71.39 to -31.15)	-1.02	<0.01

Table 2 details the clinical distribution of various characteristics in both the keratoconus and non-keratoconus groups, providing a comparative overview of anthropometric, biochemical, and corneal parameters.

The analysis revealed no statistically significant differences between the two groups for Body Mass Index (BMI) and Fasting Blood Glucose (FBS) levels. The mean BMI for keratoconus patients was 23.69 ± 5.35 kg/m^2, compared to 24.21 ± 4.97 kg/m^2 for the non-keratoconus group (p = 0.62). Similarly, fasting blood glucose levels were 4.71 ± 2.19 mmol/L in keratoconus patients and 4.92 ± 2.75 mmol/L in the control group (p = 0.68).

Regarding lipid profiles, while total cholesterol (204.76 ± 62.59 mg/dL in keratoconus vs. 178.38 ± 76.33 mg/dL in controls (Non-Keratoconus patients), p = 0.07) and triglycerides (136.58 ± 79.12 mg/dL in keratoconus vs. 118.93 ± 71.48 mg/dL in controls (Non-Keratoconus patients), p = 0.26) were numerically higher in the keratoconus group, these differences did not reach statistical significance. High-density lipoprotein levels were lower in the keratoconus group (36.17 ± 16.62 mg/dL) compared to the non-keratoconus group (41.31 ± 18.11 mg/dL), but this difference was also not statistically significant (p = 0.09).

Crucially, a statistically significant difference was observed in low-density lipoprotein levels. Keratoconus patients exhibited a mean LDL level of 112.86 ± 36.34 mg/dL, which was significantly higher than the 97.78 ± 31.89 mg/dL found in the non-keratoconus group (p = 0.03).[2] This finding suggests a potential association between elevated LDL levels and keratoconus.

Furthermore, key corneal parameters demonstrated highly significant differences between the groups. Maximum keratometry was substantially higher in keratoconus patients (57.41 ± 5.17 D) compared to controls (Non-Keratoconus patients) (46.19 ± 3.61 D), with a p-value of <0.01. Conversely, central corneal pachymetry was significantly lower in the keratoconus group (481.32 ± 56.33 μm) compared to the non-keratoconus group (532.59 ± 42.37 μm), also with a p-value of <0.01. These significant differences in K-max and pachymetry are consistent with the characteristic corneal steepening and thinning associated with keratoconus.

The result suggests that while BMI and fasting blood glucose levels are similar between age and gender-matched keratoconus and non-keratoconus groups, there are statistically significant differences in K-max, pachymetry, and notably, LDL levels.

Discussion

The observed elevation in LDL levels within the keratoconus cohort aligns with previous research indicating a potential link between altered lipid metabolism and the pathogenesis of the disease. Specifically, a meta-analysis has identified LDL levels ≥ 110 mg/dL as a significant risk factor for keratoconus, with an odds ratio of 3.00, underscoring its predictive value. This increased oxidative stress, often linked to elevated LDL, may exacerbate the corneal degradation processes characteristic of keratoconus. Furthermore, the association between elevated LDL and keratoconus suggests a systemic component to the disease, moving beyond its traditional classification as solely an ocular disorder. This systemic perspective is further supported

by evidence highlighting the role of systemic inflammatory markers in keratoconus, suggesting that compromised metabolic pathways may contribute to corneal ectasia.[2]

Importantly, beyond statistical significance ($p = 0.03$), the standardized effect size for LDL (Cohen's $d = 0.44$) in the present study indicates a small-to-moderate magnitude difference between keratoconus and control groups. This suggests that while the elevation in LDL is not large, it represents a clinically meaningful shift rather than a trivial statistical fluctuation. The 95% confidence interval (1.16 to 29.00 mg/dL) further supports the presence of a true positive association, although the moderate effect size indicates that LDL is likely one contributing factor among multiple systemic and local drivers of keratoconus pathophysiology.

Previous studies, while examining various lipid-derived metabolites, have not consistently found significant variations in cholesterol or related compounds between keratoconus patients and healthy controls (Non-Keratoconus patients).[15,16] However, the current study's robust finding of significantly elevated LDL levels in keratoconus patients, even after controlling for potential confounders, reinforces the need for further investigation into the precise mechanisms linking dyslipidemia and corneal health.

In contrast, other lipid parameters (total cholesterol, triglycerides, and HDL) demonstrated only small effect sizes (Cohen's d ranging from 0.23 to 0.38), despite some approaching statistical significance. These small magnitudes suggest limited practical impact and may reflect insufficient statistical power rather than true absence of association. The negligible effect sizes observed for BMI and fasting blood glucose further indicate that generalized metabolic disturbance was not a dominant differentiating factor in this cohort, thereby strengthening the specificity of the LDL finding.

The inflammatory component of keratoconus, characterized by increased levels of pro-inflammatory cytokines and reduced anti-inflammatory mediators in tears, may be influenced by systemic oxidative stress and metabolic alterations like dyslipidemia.[17,18] These systemic inflammatory responses, evidenced by elevated Neutrophil-Lymphocyte Ratio (NLR), Systemic Immune Inflammation Index (SII), and Platelet-Lymphocyte Ratio (PLR) in keratoconus patients, contribute to the chronic inflammatory state that can drive corneal thinning and progression.[17] Such systemic inflammation, initially believed to be absent in keratoconus, is now recognized as a critical factor in its pathogenesis, involving both local and systemic pro-inflammatory mediators.[17,19]

The magnitude of effect observed for classical corneal parameters was markedly larger, with very large effect sizes for K-max ($d \approx 2.50$) and central pachymetry ($d \approx 1.02$), confirming strong structural differentiation between groups. The contrast between these very large corneal effects and the modest biochemical effect sizes further supports the interpretation that dyslipidemia may function as a contributory systemic modifier rather than a primary structural determinant of keratoconus.

The recognition of keratoconus as a condition influenced by systemic factors, rather than a purely localized corneal pathology, opens new avenues for understanding its complex etiology and developing comprehensive management strategies.[19] This paradigm shift emphasizes the importance of a holistic approach to patient care, integrating metabolic and inflammatory evaluations into routine ophthalmological assessments for keratoconus patients. This integration could potentially lead to the identification of novel biomarkers for early detection and therapeutic targets aimed at mitigating disease progression, particularly given the growing evidence of inflammatory processes in keratoconus.[20,21,22]

This expanded understanding positions keratoconus as a systemic disorder with ocular manifestations, where chronic inflammation and dyslipidemia may act as synergistic drivers of corneal remodeling and ectasia.[6,23] This broader perspective on keratoconus's pathophysiology, encompassing systemic metabolic and inflammatory factors, aligns with emerging evidence that implicates immune dysregulation in the disease's progression.[21,24,25]Given this intricate interplay, future research should delve into the specific molecular pathways through which elevated LDL contributes to corneal inflammation and subsequent remodeling (e.g., through formation of oxidized LDL, interaction with corneal cells, impact on collagen cross-linking) in keratoconus, potentially identifying targets for systemic therapeutic interventions. Investigating the genetic predispositions to both dyslipidemia and keratoconus could further elucidate common pathways and shared risk factors.[26] Such investigations could uncover novel targets for precision medicine, tailoring interventions to the individual patient's metabolic and genetic profile to halt or even reverse keratoconus progression.

The findings of the present cross-sectional comparative study align with and expand upon existing literature regarding demographic characteristics, corneal parameters, and potential systemic associations with keratoconus.

Consistent with numerous studies, this investigation established demographic homogeneity between the keratoconus and control groups, with no statistically significant differences in age or gender distribution. This meticulous matching strengthens the validity of the comparisons, ensuring that observed clinical and biochemical differences are more likely attributable to keratoconus itself rather than confounding demographic variables.[17,27-35] For instance, a study on the inflammatory profile of keratoconic corneal epithelium also reported no significant differences in mean age or gender between keratoconus and control groups.[5] Similarly, in a study on keratoconus risk factors, ensured age and sex matching of participants.[2]

The results regarding corneal parameters are in strong agreement with the established understanding of keratoconus. We observed significantly higher maximum keratometry values and significantly lower central corneal pachymetry in keratoconus patients compared to healthy controls (Non-Keratoconus patients). This aligns with the defining features of keratoconus, characterized by progressive corneal steepening and thinning.[2,8,33] Studies utilizing advanced imaging techniques consistently report similar significant differences in corneal curvature and thickness between keratoconic and normal eyes, emphasizing these parameters as crucial diagnostic indicators.[33,34] For instance, a study reported significantly higher curvature values and lower thickness values in keratoconus eyes compared to healthy controls (Non-Keratoconus patients), mirroring the findings.[33] Another study also found significant differences in corneal curvature, asphericity, and elevation values in keratoconus patients compared to controls (Non-Keratoconus patients).[28]

A particularly notable finding in the study is the statistically significant elevation of low-density lipoprotein levels in keratoconus patients compared to the control group. This finding is supported by other research, which identified elevated serum LDL levels (≥ 110 mg/dL) as a significant risk factor for keratoconus, reporting a three-fold increased risk for individuals with such levels.[2] This further supports the potential association between altered lipid metabolism and the pathogenesis of the disease.

The broader literature widely acknowledges that keratoconus, while traditionally considered non-inflammatory, involves significant inflammatory and oxidative stress pathways.[3,4,19-26,35] Recent research indicates elevated local and systemic pro-inflammatory mediators and oxidative stress markers in keratoconus patients.[2,4,6,17,18,35] For example, studies have shown that oxidative stress is related to lipid peroxidation and inflammation, which are involved in the progression of anterior ocular diseases like keratoconus.[35] The elevated serum LDL level observed in our study is particularly relevant as high serum LDL is known to increase the risk of oxidative stress, and oxidized LDL can trigger inflammatory reactions. This finding, therefore, adds evidence supporting an inflammatory background in keratoconus and suggests that elevated serum LDL levels could be a risk factor for the condition.[2] This systemic perspective is further supported by evidence highlighting the role of systemic inflammatory markers, such as increased neutrophil/lymphocyte ratio, systemic immune-inflammation index, and platelet/lymphocyte ratio, which are recognized indicators of systemic inflammation and have been found elevated in keratoconus patients.[6,17,18]

In summary, this study reinforces established clinical findings regarding corneal morphology in keratoconus. Critically, it also presents compelling evidence for an association between elevated serum LDL levels and the condition, a finding corroborated by other recent investigations.[2] This observation highlights the potential role of systemic metabolic factors, particularly those related to oxidative stress and inflammation, in the complex etiology of keratoconus. Future research should aim to further elucidate the precise mechanisms by which elevated LDL may contribute to corneal changes and keratoconus progression, and investigate its utility as a potential biomarker or therapeutic target.

Limitations of the study

Despite the significant association found between elevated serum LDL and keratoconus, several limitations of this study must be acknowledged.

First, the cross-sectional design inherently limits the ability to establish a definitive causal relationship between dyslipidemia and the development or progression of keratoconus. While we observed higher LDL levels in the keratoconus group, longitudinal studies

are required to determine if lipid profile alterations precede corneal changes or if they are concurrent markers of a broader systemic inflammatory state.

Second, the sample size, while statistically adequate for the primary outcome, may have been insufficient to detect smaller but potentially clinically significant differences in other lipid parameters, such as total cholesterol or high-density lipoprotein, which showed numerical but non-significant trends.

Third, as a single-center study conducted in an urban specialized eye hospital, the findings may not be fully representative of the general population or different ethnic groups.

Finally, while we excluded major systemic diseases, other potential confounding factors such as dietary habits, physical activity levels, and specific genetic predispositions for dyslipidemia were not exhaustively controlled for, which could influence serum lipid concentrations. Future multi-center, prospective studies with larger cohorts and more comprehensive metabolic profiling are necessary to further validate these findings and explore the underlying pathophysiological mechanisms.

Conclusion

This cross-sectional comparative study provides significant insights into the association between elevated serum low-density lipoprotein levels and keratoconus, suggesting that systemic metabolic factors, particularly those linked to oxidative stress and inflammation, may play a crucial role in its pathogenesis. The findings suggest that monitoring and managing dyslipidemia could be a relevant consideration in the comprehensive care of keratoconus patients, offering a novel avenue for therapeutic intervention or risk stratification. Further longitudinal studies to track LDL changes and keratoconus progression and also investigation into the precise mechanisms through which elevated LDL contributes to the progression of corneal ectasia and whether lipid-lowering therapies could modulate disease trajectory is warranted.

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