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Remnant Cholesterol and Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

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Research Article

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Abstract

Purpose

Diabetic retinopathy is a leading cause of visual impairment in patients with diabetes mellitus. Because the association between conventional lipid parameters and diabetic retinopathy remains inconsistent, attention has shifted toward alternative lipid markers such as remnant cholesterol. Recent studies in type 2 diabetes suggest that higher remnant cholesterol levels may be associated with diabetic retinopathy. This study aimed to assess the association between remnant cholesterol and diabetic retinopathy in patients with type 2 diabetes mellitus.

Methods

We conducted a cross-sectional study including 100 patients with type 2 diabetes mellitus, 50 with diabetic retinopathy and 50 without diabetic retinopathy. Remnant cholesterol was calculated as total cholesterol minus low-density lipoprotein cholesterol minus high-density lipoprotein cholesterol. Clinical, biological, and lipid parameters were compared between groups. Multivariable logistic regression and receiver operating characteristic curve analyses were performed.

Results

Remnant cholesterol did not differ significantly between patients with and without diabetic retinopathy (0.62 [0.50–0.90] vs 0.67 [0.51–1.02] mmol/L, p = 0.627). No significant difference in remnant cholesterol was observed across diabetic retinopathy stage categories (p = 0.591). Microalbuminuria was more frequent in patients with diabetic retinopathy (44% vs 20%, p = 0.018), and median microalbuminuria values were significantly higher (40.48 [12.38–96.50] vs 14.79 [9.98–28.48], p = 0.009). In multivariable analysis adjusted for age, sex, diabetes duration, HbA1c, hypertension, and microalbuminuria, remnant cholesterol was not independently associated with diabetic retinopathy (adjusted OR 0.63, 95% CI 0.25–1.62, p = 0.342), whereas microalbuminuria remained independently associated (adjusted OR 2.93, 95% CI 1.16–7.40, p = 0.023). Receiver operating characteristic analysis showed poor discriminatory performance of remnant cholesterol (AUC = 0.53).

Conclusion

Remnant cholesterol was not significantly associated with the presence or severity of diabetic retinopathy in this cohort and had limited value as a standalone marker. Microalbuminuria appeared to be more strongly associated with diabetic retinopathy than remnant cholesterol.

Introduction

Diabetic retinopathy is a leading cause of visual impairment in patients with diabetes mellitus [1]. Because the association between conventional lipid parameters and diabetic retinopathy remains inconsistent, attention has shifted toward alternative lipid markers such as remnant cholesterol [3, 5]. Recent studies in type 2 diabetes suggest that higher remnant cholesterol levels may be associated with diabetic retinopathy [7, 8, 10, 12].

The pathogenesis of diabetic retinopathy is complex and multifactorial. Chronic hyperglycemia, oxidative stress, inflammation, endothelial dysfunction, and breakdown of the blood-retinal barrier contribute to retinal microvascular injury [2, 5]. In addition to classical risk factors such as duration of diabetes, poor glycemic control, and hypertension, increasing interest has been directed toward the role of lipid abnormalities in the development and progression of diabetic retinopathy [3, 5].

Remnant cholesterol represents the cholesterol content of triglyceride-rich lipoproteins, including very-low-density lipoproteins, intermediate-density lipoproteins, and chylomicron remnants [4]. It can be easily calculated from the standard lipid profile as total cholesterol minus low-density lipoprotein cholesterol minus high-density lipoprotein cholesterol [4]. Remnant cholesterol is increasingly recognized as an atherogenic lipid fraction and has been associated with cardiometabolic risk and vascular complications in patients with diabetes [4, 9, 11].

However, the available evidence remains limited and not entirely consistent across populations [6–8, 10, 12]. The present study aimed to assess the association between remnant cholesterol and diabetic retinopathy in patients with type 2 diabetes mellitus and to evaluate its relationship with diabetic retinopathy severity as well as other clinical and biological factors.

Methods

This was a monocentric, cross-sectional analytical study conducted in the Department of Endocrinology of the Military Principal Hospital of Instruction of Tunis, Tunisia, from July 2025 to January 2026. Adult patients with type 2 diabetes mellitus who were either hospitalized in the endocrinology department or followed in the outpatient clinic were eligible for inclusion.

Patients were excluded when retinal examination was not feasible, when another ophthalmologic disease other than diabetic retinopathy was present, or in the case of another type of diabetes, thyroid dysfunction, liver failure, systemic disease, or chronic inflammatory disease. Participants were divided into two matched groups according to age, sex, and diabetes duration: patients with diabetic retinopathy and patients without diabetic retinopathy.

Clinical, biological, and ophthalmological data were collected using a pre-established form. Lipid parameters were measured, and remnant cholesterol was calculated as total cholesterol minus LDL cholesterol minus HDL cholesterol. Additional laboratory parameters included fasting glucose, HbA1c, and 24-hour microalbuminuria.

Ophthalmologic assessment included seven-field stereoscopic fundus photography, fluorescein angiography, and optical coherence tomography when indicated. Diabetic retinopathy severity was classified according to the international clinical grading scale.

Statistical analysis was performed using SPSS version 26. Quantitative variables were compared using Student's t-test or the Mann-Whitney U test as appropriate, whereas qualitative variables were compared using Pearson's chi-square test or Fisher's exact test. Binary logistic regression was used to identify independent predictors of diabetic retinopathy, and ROC curve analysis assessed the predictive performance of remnant cholesterol.

Results

A total of 100 patients with type 2 diabetes mellitus were included, comprising 50 patients with diabetic retinopathy and 50 without diabetic retinopathy. The two groups were comparable in age (62.20 ± 9.26 vs 61.82 ± 9.58 years, p = 0.841), sex distribution (52% women and 48% men in each group, p = 1.000), diabetes duration (14.00 [10.00–19.00] vs 12.50 [10.00-19.75] years, p = 0.435), HbA1c (10.76 ± 2.47 vs 10.26 ± 2.41%, p = 0.310), and history of hypertension (72% vs 56%, p = 0.145) (Table 1**)**.

No significant difference was found between patients with and without diabetic retinopathy for conventional lipid parameters. Total cholesterol was 4.15 [3.62–5.17] mmol/L in patients with diabetic retinopathy versus 4.60 [3.80–5.47] mmol/L in those without diabetic retinopathy (p = 0.225). Triglycerides were 1.39 [1.10–2.08] vs 1.46 [1.10–2.26] mmol/L (p = 0.689), LDL cholesterol 2.37 [1.95–3.20] vs 2.58 [1.92–3.55] mmol/L (p = 0.275), HDL cholesterol 1.08 [0.91–1.31] vs 1.10 [1.01–1.25] mmol/L (p = 0.627), and remnant cholesterol 0.62 [0.50–0.90] vs 0.67 [0.51–1.02] mmol/L (p = 0.627) (Table 2**)**.

Microalbuminuria was more frequent in the diabetic retinopathy group (44% vs 20%, p = 0.018), and median microalbuminuria values were significantly higher (40.48 [12.38–96.50] vs 14.79 [9.98–28.48], p = 0.009). Diabetic neuropathy (64% vs 14%, p < 0.001), macroangiopathy (52% vs 22%, p = 0.004), coronary artery disease (44% vs 20%, p = 0.018), and peripheral arterial disease (16% vs 2%, p = 0.031) were also significantly more frequent among patients with diabetic retinopathy **(**Table 1**)**.

Table 1
Baseline clinical and biological characteristics of patients with and without diabetic retinopathy

Variable	Diabetic retinopathy (n = 50)	No diabetic retinopathy (n = 50)	p value
Age, years	62.20 ± 9.26	61.82 ± 9.58	0.841
Sex, women/men, n	26 / 24	26 / 24	1.000
Duration of diabetes, years	14.00 [10.00–19.00]	12.50 [10.00-19.75]	0.435
HbA1c, %	10.76 ± 2.47	10.26 ± 2.41	0.310
Hypertension, n (%)	36 (72%)	28 (56%)	0.145
Microalbuminuria present, n (%)	22 (44%)	10 (20%)	0.018
Microalbuminuria, mg/24 h	40.48 [12.38–96.50]	14.79 [9.98–28.48]	0.009
Diabetic neuropathy, n (%)	32 (64%)	7 (14%)	< 0.001
Macroangiopathy, n (%)	26 (52%)	11 (22%)	0.004
Coronary artery disease, n (%)	22 (44%)	10 (20%)	0.018
Peripheral arterial disease, n (%)	8 (16%)	1 (2%)	0.031

Table 2
Lipid profile and remnant cholesterol according to diabetic retinopathy status

Variable	Diabetic retinopathy (n = 50)	No diabetic retinopathy (n = 50)	p value
Total cholesterol, mmol/L	4.15 [3.62–5.17]	4.60 [3.80–5.47]	0.225
Triglycerides, mmol/L	1.39 [1.10–2.08]	1.46 [1.10–2.26]	0.689
LDL cholesterol, mmol/L	2.37 [1.95–3.20]	2.58 [1.92–3.55]	0.275
HDL cholesterol, mmol/L	1.08 [0.91–1.31]	1.10 [1.01–1.25]	0.627
Remnant cholesterol, mmol/L	0.62 [0.50–0.90]	0.67 [0.51–1.02]	0.627

Among patients with diabetic retinopathy, remnant cholesterol did not significantly differ according to diabetic retinopathy stage categories (p = 0.591). In multivariable logistic regression adjusted for age, sex, diabetes duration, HbA1c, hypertension, and microalbuminuria, remnant cholesterol was not independently associated with diabetic retinopathy (adjusted OR 0.63, 95% CI 0.25–1.62, p = 0.342), whereas microalbuminuria remained independently associated with diabetic retinopathy (adjusted OR 2.93, 95% CI 1.16–7.40, p = 0.023) (Table 3**)**. Receiver operating characteristic analysis showed poor discriminatory performance of remnant cholesterol (AUC = 0.53) (Fig. 1**)**.

Table 3
Multivariable logistic regression analysis of factors associated with diabetic retinopathy

Variable	Adjusted OR	95% CI	p value
Microalbuminuria	2.93	1.16–7.40	0.023
Remnant cholesterol	0.63	0.25–1.62	0.342
Adjusted covariates	Age, sex, duration of diabetes, HbA1c, hypertension	—	—

Discussion

In the present study, remnant cholesterol was not significantly associated with the presence of diabetic retinopathy in patients with type 2 diabetes mellitus. Remnant cholesterol levels were similar in patients with and without diabetic retinopathy, did not differ significantly across diabetic retinopathy stages, and showed poor discriminatory performance on ROC curve analysis. Furthermore, remnant cholesterol was not independently associated with diabetic retinopathy after adjustment for age, sex, duration of diabetes, HbA1c, hypertension, and microalbuminuria.

These findings do not support remnant cholesterol as a useful standalone marker of diabetic retinopathy in our cohort. This result contrasts with the growing body of literature suggesting a potential role of remnant cholesterol in diabetic microvascular disease [6–8, 10, 12]. Shan et al. reported that higher remnant cholesterol levels were associated with diabetic retinopathy in patients with type 2 diabetes mellitus [7]. Similarly, Pan et al. described a non-linear relationship between remnant cholesterol and diabetic retinopathy in a cross-sectional diabetic population [8]. More recently, Chen et al. found that remnant cholesterol was correlated with both retinal vascular morphology and diabetic retinopathy in patients with type 2 diabetes mellitus [10]. In addition, Wei et al. reported an association between the remnant cholesterol/high-density lipoprotein cholesterol ratio and diabetic retinopathy [12]. However, our results suggest that this association may not be consistent across all populations and clinical settings.

Several explanations may account for the discrepancy between our findings and those reported in previous studies. First, the cross-sectional design only captures lipid exposure at a single point in time and does not reflect the cumulative burden of remnant cholesterol over the course of diabetes. Second, remnant cholesterol may be more closely associated with broader cardiometabolic or renal risk than with retinal disease specifically [6, 9, 11]. Indeed, remnant cholesterol has also been linked to incident type 2 diabetes and chronic kidney disease, supporting its role as a marker of systemic metabolic and vascular dysfunction rather than a specific retinal marker [9, 11].

An important finding of our study was the strong association between microalbuminuria and diabetic retinopathy. Microalbuminuria was more frequent and quantitatively higher in patients with diabetic retinopathy, and it remained independently associated with diabetic retinopathy in multivariable analysis. This observation is consistent with the concept that diabetic retinopathy and albuminuria are parallel manifestations of generalized microvascular injury [2, 5, 13]. Chronic hyperglycemia, endothelial

dysfunction, inflammation, and oxidative stress may simultaneously affect the retinal and renal microcirculation, explaining the frequent coexistence of these complications [2, 5].

We also found that diabetic neuropathy, macroangiopathy, coronary artery disease, and peripheral arterial disease were significantly more frequent in the retinopathy group. These findings suggest that diabetic retinopathy clustered with a broader burden of vascular disease in our population. This is biologically plausible and in line with the current understanding of diabetic retinopathy as part of a systemic microvascular and macrovascular disease process rather than an isolated ocular condition [2, 5, 13].

The lack of significant association between conventional lipid parameters and diabetic retinopathy in our study is also noteworthy. Previous reviews have emphasized that the contribution of dyslipidemia to diabetic retinopathy is complex and remains incompletely understood [3, 5]. Although dyslipidemia may contribute to retinal exudation, inflammation, and endothelial injury, conventional serum lipid levels have not consistently shown strong associations with diabetic retinopathy across studies [3]. Our findings are in agreement with this heterogeneous literature and suggest that, in our cohort, lipid abnormalities were less informative than renal and vascular markers.

Our study has several strengths. It addressed a clinically relevant question using routinely available biochemical measurements and a standardized ophthalmologic evaluation based on established classification systems [1]. It also explored not only the binary association between remnant cholesterol and diabetic retinopathy but also the relationship with disease severity and the diagnostic performance of remnant cholesterol.

However, some limitations should be acknowledged. This was a single-center study with a relatively limited sample size. Its cross-sectional design precludes any causal inference. Residual confounding cannot be excluded. In addition, treatment-related variables, especially lipid-lowering therapy, were not incorporated into the analysis and may have influenced lipid values.

Overall, our findings suggest that remnant cholesterol has limited utility as an isolated biomarker of diabetic retinopathy in this population. In contrast, microalbuminuria appeared to be more strongly associated with diabetic retinopathy than remnant cholesterol. Larger multicenter prospective studies are needed to clarify whether remnant cholesterol has incremental value when combined with established clinical and biological markers [6–8, 10, 12].

Conclusion

In this cross-sectional study of patients with type 2 diabetes mellitus, remnant cholesterol was not significantly associated with the presence or severity of diabetic retinopathy and showed poor diagnostic performance. By contrast, microalbuminuria was independently associated with diabetic retinopathy. These findings suggest that remnant cholesterol has limited utility as an isolated biomarker of diabetic retinopathy in this setting.

Declarations

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Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Najla Bchir and Youssef Gharbi. The first draft of the manuscript was written by Najla Bchir, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Military Principal Hospital of Instruction of Tunis.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent to publish: Not applicable.

Data Availability: The datasets generated and/or analyzed during the current study are not publicly available because they contain potentially identifiable clinical data but are available from the corresponding author on request.

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Figures

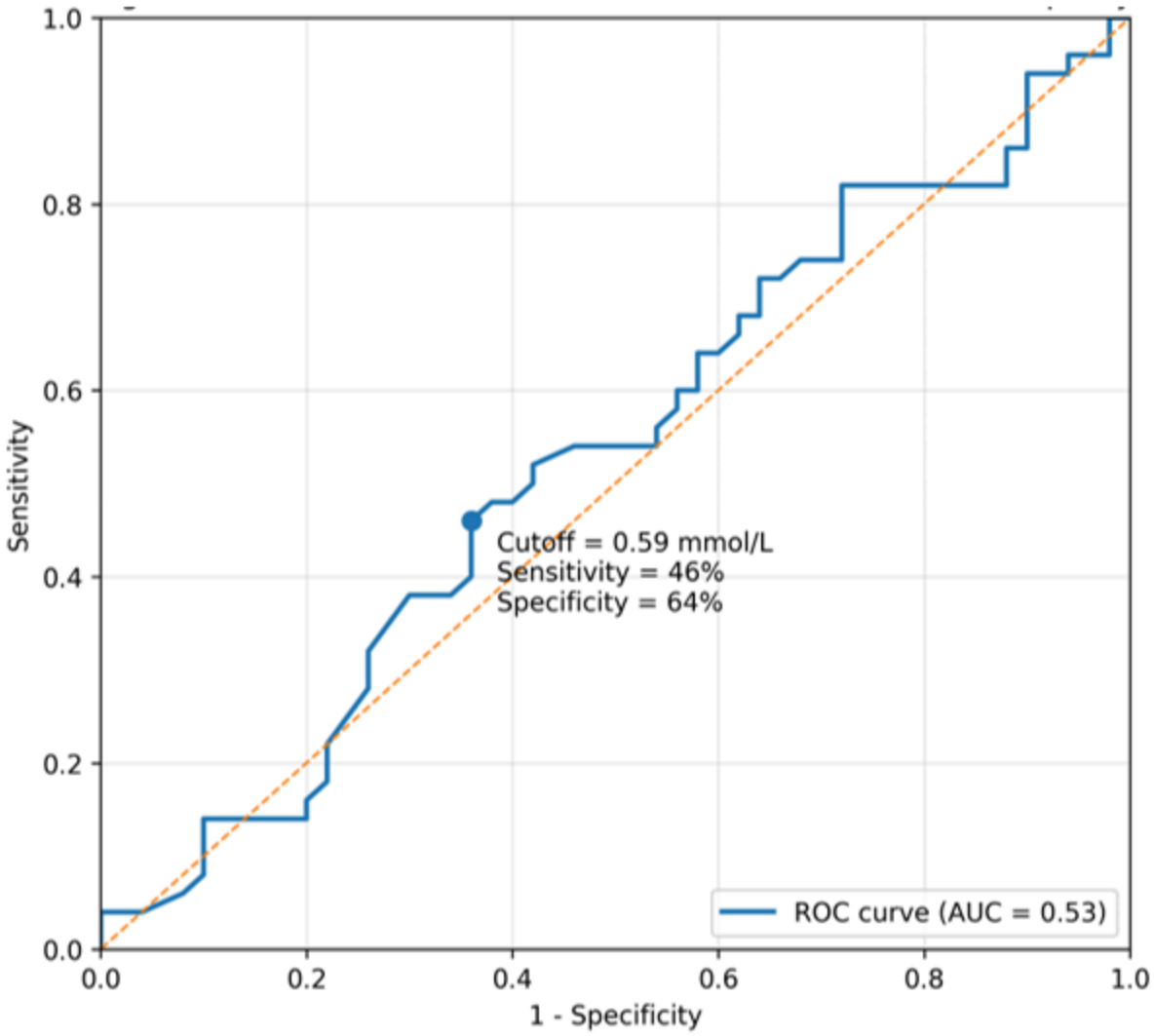


Figure 1

Receiver operating characteristic curve of remnant cholesterol for diabetic retinopathy