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Glycated LDL as a marker of erectile dysfunction severity in diabetes: evidence for a role of metabolic memory

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Abstract

Erectile dysfunction (ED) is a common complication of type 2 diabetes mellitus and is closely linked to endothelial dysfunction and metabolic disturbances. However, the relationship between glycemic control and ED severity remains inconsistent, suggesting that cumulative metabolic injury may play a more important role. In this cross-sectional comparative study, 60 diabetic patients with ED and 60 age-matched healthy controls were evaluated. ED severity was assessed using the International Index of Erectile Function-5 (IIEF-5), and patients were stratified according to ED severity and glycemic control (HbA1c <7% vs. ≥7%). Circulating glycated low-density lipoprotein (g-LDL) levels were significantly higher in patients with ED compared to controls ($p < 0.001$) and increased progressively with ED severity ($\eta^2 = 0.39$). In multivariable analysis, g-LDL (OR = 1.014, $p = 0.003$) and duration of diabetes (OR = 1.041, $p = 0.008$) were identified as independent predictors of ED severity, whereas HbA1c was not. Despite significant differences in HbA1c between controlled and uncontrolled diabetic groups ($p = 0.009$), no differences were observed in g-LDL levels or erectile function scores, while strong group effects were observed for g-LDL ($\eta^2 = 0.76$) and IIEF ($\eta^2 = 0.80$). These findings indicate that g-LDL is strongly associated with ED severity and may reflect cumulative metabolic injury more effectively than HbA1c, supporting the concept that long-term metabolic burden contributes to the pathogenesis of diabetic ED in line with mechanisms related to metabolic memory.

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity and affects at least 50% of men with diabetes mellitus, with a prevalence that is approximately threefold higher than in men without diabetes [1].Diabetic erectile dysfunction is fundamentally characterized by cavernosal endothelial dysfunction, as a healthy endothelium is essential for regulating penile vascular tone. Chronic hyperglycaemia promotes the accumulation of advanced glycation end-products (AGEs), which reduce nitric oxide (NO) bioavailability and increase oxidative stress in endothelial cells. In addition, decreased expression and activity of endothelial nitric oxide synthase (eNOS) further impair vasodilation, ultimately leading to a compromised erectile response [2–4].Glycemic memory is defined as the persistence of diabetic complications despite the achievement of pharmacological glycemic control and represents the clinical manifestation of the broader concept of metabolic memory [5, 6]. This phenomenon indicates that prior hyperglycemic exposure exerts lasting effects even after glycemic levels are improved [6]. At the molecular level, metabolic memory is driven by hyperglycemia-induced pathways, particularly the accumulation of AGEs and increased production of reactive oxygen species, which lead to sustained cellular damage and perpetuate this “memory” [7].

Glycated low-density lipoprotein (g-LDL), formed under hyperglycemic conditions, plays a critical role in the development of endothelial dysfunction in diabetes. Glycation-induced structural alterations of apolipoprotein B impair LDL receptor–mediated clearance and increase its susceptibility to oxidative modification, thereby promoting intracellular lipid accumulation, foam cell formation, and accelerated

atherogenesis. Furthermore, g-LDL directly disrupts endothelial function by reducing endothelial nitric oxide synthase (eNOS) expression and nitric oxide (NO) bioavailability, while increasing oxidative stress, inflammatory signaling, and monocyte adhesion. These alterations shift endothelial cells toward a pro-inflammatory, pro-thrombotic, and vasoconstrictive phenotype, ultimately contributing to vascular dysfunction and the pathogenesis of diabetic erectile dysfunction [8].

Although previous studies have demonstrated the role of g-LDL in the development of atherosclerosis [9], data on the association between g-LDL and ED severity remain limited. Therefore, this study aimed to investigate the relationship between circulating gLDL levels and ED severity, and to explore the role of gLDL as a reflection of metabolic memory contributing to the pathogenesis of ED.

Materials and Methods

Study Design and Participants

This cross-sectional comparative study utilised prospectively collected data and included 60 patients who presented to the andrology outpatient clinic with ED and had a diagnosis of type 2 diabetes mellitus for a minimum of 10–15 years. Concurrently, a control group of 60 age-matched healthy males was recruited. The control group was used to evaluate metabolic memory by enabling comparisons with subgroups of diabetic patients stratified according to glycemic control status. Glycemic control was defined based on HbA1c levels, with values <7% indicating controlled diabetes [10].

A post-hoc power analysis was performed to determine the required sample size to detect a between-group difference with 80% power at a 5% significance level, using g-LDL levels as the primary endpoint. The analysis confirmed that a total sample size of 120 participants (60 per group) was sufficient.

Demographic and Biochemical Measurements

Demographic and biochemical parameters recorded included age, fasting plasma glucose, glycated hemoglobin (HbA1c), triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total testosterone levels, and waist circumference (WC). Body mass index (BMI) was calculated as weight (kg)/height² (m²).

Blood samples were obtained after overnight fasting, and serum samples were separated and stored at −80°C until analysis. Circulating g-LDL levels were measured using a commercially available human ELISA kit (E-EL-H5561, Elabscience, Houston, TX, USA) according to the manufacturer's instructions. All measurements were performed in duplicate, and mean values were used for analysis. Other laboratory parameters were analysed using standard methods in the hospital's central laboratory.

Assessment of Erectile Function

Erectile function was assessed using the validated International Index of Erectile Function-5 (IIEF-5) questionnaire. Scores range from 5 to 25, with lower scores indicating more severe dysfunction. ED

severity was categorised as follows: 5–7 severe, 8–11 moderate, 12–16 mild to moderate, 17–21 mild, and 22–25 no ED [11].

In addition, erectile function was objectively evaluated using intracavernosal alprostadil injection combined with visual sexual stimulation, and erection rigidity was assessed using the Erection Hardness Score (EHS)

Exclusion Criteria

Patients with a history of pelvic or penile surgery, trauma, or congenital anomalies affecting erectile function were excluded. Individuals using medications that could affect sexual function, including phosphodiesterase type 5 inhibitors (PDE-5i), antiandrogens, or testosterone therapy, were excluded unless a wash-out period of at least 4 weeks had been completed.

Patients receiving lipid-lowering therapies such as statins or fibrates were excluded. Additionally, individuals with severe systemic diseases, including advanced liver or renal disease, uncontrolled hypertension, or heart failure, as well as those with active inflammatory, infectious, or psychiatric disorders, were excluded.

Patients with non-diabetic hormonal disorders or uncontrolled metabolic conditions that could influence g-LDL levels were also excluded to ensure that the observed associations specifically reflected the relationship between g-LDL and ED severity.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 27; IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test, which indicated that the data were not normally distributed ($p < 0.05$). Accordingly, continuous variables were expressed as median (interquartile range, IQR), and non-parametric tests were applied.

Comparisons between two groups were performed using the Mann–Whitney U test, while comparisons among three or more groups were conducted using the Kruskal–Wallis test. Effect sizes for non-parametric comparisons were estimated using eta-squared (η^2), calculated from the Kruskal–Wallis H statistic to assess the magnitude of group differences. When a significant difference was detected, post hoc pairwise comparisons were performed using Bonferroni correction.

Categorical variables were analyzed using the chi-square test. To identify independent factors associated with erectile dysfunction severity, ordinal logistic regression analysis was performed. Model fit was assessed using Nagelkerke R^2, and the proportional odds assumption was evaluated using the test of parallel lines. Multicollinearity was assessed using variance inflation factor (VIF), and no significant multicollinearity was detected ($VIF < 5$).

A p-value < 0.05 was considered statistically significant in all analyses.

Results

The study comprised a total of 60 patients diagnosed with ED and 60 age-matched healthy subjects. There were no significant differences between the two groups with regard to age or BMI, indicating comparable baseline demographic characteristics. However, patients diagnosed with ED exhibited significantly higher levels of LDL cholesterol, triglycerides, fasting plasma glucose, HbA1c, and circulating g-LDL compared to the control group. Conversely, HDL levels were lower in the ED group, while total testosterone levels remained comparable between groups. Furthermore, the duration of diabetes was recorded exclusively within the patient group. Erectile function was assessed using the IIEF-5 questionnaire, and the results indicated a significant reduction in erectile function in patients with ED compared to the control group (Table 1).

The relationship between clinical and biochemical parameters and the severity of ED was evaluated using the Kruskal–Wallis test. A range of significant differences were identified across ED severity groups in relation to LDL cholesterol, triglycerides, g-LDL levels, and duration of diabetes (all $p = 0.001$). Notably, g-LDL exhibited a substantial effect size ($\eta^2 = 0.39$), corresponding to a moderate-to-large effect. Among all evaluated parameters, g-LDL demonstrated a consistent and progressive increase across ED severity groups, following a stepwise pattern. Subsequent post hoc analyses revealed that LDL and triglyceride levels were significantly higher in patients with severe ED compared to other groups. In a similar manner, levels of g-LDL increased progressively with the severity of ED, with significantly higher levels observed in moderate and severe ED compared to milder forms. Furthermore, an increased duration of diabetes was associated with a more severe presentation of ED.

Conversely, age, testosterone levels, and fasting glucose levels did not demonstrate a significant correlation with the severity of ED. Despite the significance of BMI and HDL levels in overall comparisons, no significant pairwise differences were observed. The HbA1c test demonstrated a borderline association with the severity of ED, yet it did not attain statistical significance ($p = 0.057$) (Table 2a) and was not identified as an independent predictor in regression analysis. Furthermore, the severity of ED was found to vary significantly according to the subjects' hypertension and smoking status. Patients diagnosed with hypertension and smokers were more likely to present with moderate-to-severe ED compared to non-hypertensive and non-smoking individuals ($p = 0.017$ and $p = 0.009$, respectively) (Table 2b).

An ordinal logistic regression analysis was performed in order to ascertain the independent predictors of ED severity. It was established that among the variables included in the model, circulating g-LDL levels and duration of diabetes emerged as significant independent predictors of ED severity. Specifically, higher levels of g-LDL were found to be associated with increased odds of more severe ED (odds ratio [OR] = 1.014, 95% confidence interval [CI]: 1.005–1.024, $p = 0.003$), while a longer duration of diabetes was also found to be significantly associated with ED severity (OR = 1.041, 95% CI: 1.011–1.072, $p = 0.008$). In contrast, HbA1c, hypertension, and smoking status were not independently associated with ED severity in the multivariable model, although smoking showed a borderline trend ($p = 0.068$) (Table 3). No

significant multicollinearity was detected among the variables included in the model (all VIF values < 5), indicating model stability. The proportional odds assumption was satisfied ($p > 0.05$), confirming the validity of the ordinal regression model.

A comparative analysis was conducted among healthy controls, patients with controlled diabetes, and those with uncontrolled diabetes. This analysis revealed significant differences across the groups for g-LDL, HbA1c, and IIEF scores (all $p < 0.001$). The magnitude of these differences was substantial for all parameters (g-LDL $\eta^2 = 0.76$, HbA1c $\eta^2 = 0.86$, IIEF $\eta^2 = 0.80$). Subsequent post hoc analyses revealed that both diabetic groups exhibited significantly elevated levels of g-LDL compared to healthy controls (both $p < 0.001$). However, no substantial difference was observed between diabetic patients with and without glycemic control ($p = 0.156$), despite differences in glycemic status. In addition, IIEF scores were found to be significantly lower in both diabetic groups compared to the control group (both $p < 0.001$), with no significant difference observed between the controlled and uncontrolled groups ($p = 0.338$). In contrast, HbA1c levels exhibited a significant difference not only between diabetic patients and controls but also between controlled and uncontrolled diabetic groups ($p = 0.009$). Despite considerable variations in glycemic control, no corresponding disparities were observed in g-LDL levels or erectile function between the diabetic groups (Table 4).

Discussion

This study provides clinical evidence that circulating g-LDL levels are significantly associated with both the presence and severity of ED in patients with type 2 diabetes mellitus. The strong negative correlation observed between g-LDL levels and IIEF-5 scores suggests that increasing g-LDL levels are closely linked to worsening erectile function. These findings support the role of g-LDL not only as an atherosclerotic risk factor but also as a potential marker of endothelial injury within the penile vasculature of diabetic patients.

ED is highly prevalent among individuals with DM, and its severity has been associated with multiple clinical and metabolic factors [12]. In our cohort, ED severity was significantly associated with longer duration of diabetes and adverse lipid parameters, particularly elevated LDL and triglyceride levels. Additionally, hypertension and smoking were more common in patients with severe ED. In contrast, no significant association was observed with age, testosterone levels, glucose, or HbA1c. Notably, g-LDL emerged as a significant metabolic marker, with levels increasing in parallel with ED severity ($p = 0.001$).

While the role of glycemic control in reducing diabetic complications is well established, its impact on ED remains unclear due to conflicting evidence in the literature [13,17]. In our study, HbA1c levels were not significantly associated with ED severity. In contrast, the observed relationship between ED severity, g-LDL levels, and duration of diabetes suggests that long-term metabolic burden, rather than momentary glycemic control, may play a more decisive role. Consistently, although HbA1c levels differed between controlled and uncontrolled diabetic groups, g-LDL levels and erectile function scores (IIEF) were comparable. These findings support the concept that normalization of glucose levels alone may not

reverse accumulated metabolic damage, in line with the concept of metabolic memory in the pathogenesis of ED.

The concept of metabolic memory suggests that early hyperglycemic exposure initiates a self-perpetuating cycle of vascular damage that persists despite subsequent optimization of glycemic control [18,20]. This phenomenon is largely mediated by sustained activation of the AGE–RAGE (receptor for AGE) axis, whereby chronic interaction between AGEs and their receptors promotes persistent vascular inflammation and endothelial dysfunction. Consequently, this pathway plays a central role in the pathogenesis of cardiovascular disease, maintaining cellular stress and “remembering” prior hyperglycemic insults [21].

In a recent retrospective case–control study, the impact of metabolic memory on disease severity and treatment response in diabetic patients with erectile dysfunction was investigated [20]. Patients were classified based on glycemic control status and treatment history into three groups: those with consistently well-controlled glycemia, those with poor glycemic control, and those with a history of poor control but subsequent improvement, defined as the “metabolic memory” group. Their results demonstrated that patients in the metabolic memory group exhibited erectile function comparable to those with persistently poor glycemic control, and both groups had worse outcomes than patients with consistently good control. However, no significant differences were observed among the groups in terms of response to PDE5 inhibitor therapy. These findings suggest that early hyperglycemic exposure may have lasting detrimental effects on erectile function, while not necessarily influencing treatment responsiveness.

In our study, comparison across healthy controls, well-controlled diabetic patients, and poorly controlled diabetic patients demonstrated that although HbA1c levels differed significantly between controlled and uncontrolled groups, no significant difference was observed in g-LDL levels or IIEF-5 between these two groups. This finding is consistent with the study by Hui et al., in which patients with a history of poor glycemic control exhibited erectile function comparable to those with persistently uncontrolled diabetes, despite subsequent improvement in glycemic status. Together, these results suggest that normalization of glycemic parameters alone may not adequately reflect the underlying metabolic burden.

Notably, in our multivariable analysis, g-LDL levels were independently associated with ED severity ($p = 0.003$), whereas no such association was observed for HbA1c. These findings suggest that g-LDL may serve as a more sensitive marker of ED severity than HbA1c and may better reflect cumulative, time-dependent metabolic damage rather than momentary glycemic status.

This study has several limitations that should be considered when interpreting the findings. First, the sample size was relatively small and derived from a single center, which may limit the generalizability of the results. Second, the cross-sectional design precludes conclusions regarding causal relationships between g-LDL levels and ED. Third, other biomarkers related to oxidative stress, endothelial dysfunction, and advanced glycation were not evaluated, which might have provided further mechanistic insight into the observed associations. Additionally, the absence of a non-diabetic ED control group limits the ability

to distinguish diabetes-specific effects from general mechanisms of erectile dysfunction. Furthermore, the lack of association between HbA1c and ED severity should be interpreted with caution given the relatively limited sample size.

Despite these limitations, the present study provides novel clinical evidence supporting the role of circulating g-LDL as a potential marker of erectile dysfunction severity in patients with diabetes mellitus.

Conclusion

This study demonstrates that circulating g-LDL levels are significantly associated with both the presence and severity of erectile dysfunction (ED) in patients with diabetes mellitus. Importantly, our findings suggest that ED is more closely linked to cumulative metabolic injury than to momentary glycemic status, highlighting the limitations of HbA1c as a sole predictor in this context. Consequently, g-LDL may serve as a promising integrative biomarker reflecting metabolic memory-related vascular damage and endothelial dysfunction. From a clinical perspective, assessing g-LDL levels could facilitate the identification of high-risk diabetic patients with subclinical vascular damage, enabling earlier and more targeted intervention strategies that extend beyond conventional glycemic control. Future large-scale prospective studies are warranted to validate these findings and to explore whether targeting lipoprotein glycation offers novel therapeutic opportunities in diabetic ED.

Declarations

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Erdal Abay obtained informed consent from the patients, informed them about the study, collected clinical histories, performed the g-LDL measurements, and organized the laboratory data. Erdal Abay and Levent Özcan wrote and designed the manuscript together. Levent Özcan revised the manuscript and carried out the statistical analysis. Alper Ötünçtemur obtained ethical approval and developed and planned the study. Emre Can Polat contributed to the discussion and assisted with the references. All authors reviewed and approved the final manuscript.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the University of Health Sciences, Hamidiye Faculty of Medicine (Date: 15 November 2021; Approval No: 56).

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Competing Interests

The authors declare that they have no competing interests. The authors report no financial or non-financial relationships that could have influenced the work reported in this study.

Informed Consent

Written informed consent was obtained from all participants.

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Tables

Table 1. Baseline characteristics of the study population

	Patients (n=60)			Controls (n=60)		
Variable	Mean±SD	Median	IQR	Mean±SD	Median	IQR
Age (years)	51.2 ± 1.5	52	51.3–52	51.6 ± 2.0	50	50–52
BMI (kg/m²)	28.1 ± 1.6	27.8	27.5–29.4	27.1 ± 2.0	27.7	26–27.8
LDL (mg/dL)	141.4 ± 11	140	140–150	100.8 ± 14.2	100	90–110
HDL (mg/dL)	39.5 ± 9.7	38.5	35–43	44.4 ± 11	42	37.3–50.8
Triglyceride (mg/dL)	160.4 ± 23.7	160	160–180	121.7 ± 25.8	130	100–140
Testosterone (ng/dL)	365.8 ± 15.2	360	360–370	372.8 ± 16.7	370	360–387.5
Glucose (mg/dL)	127.9 ± 16.1	127	115.3–140.8	82.4 ± 7.9	80	75–86
HbA1c (%)	6.9 ± 0.2	6.8	6.8–7	5.0 ± 0.2	5.2	5.2–5.3
g-LDL (ng/mL)	962.3 ± 944.5	944.5	888.2–1043	565.9 ± 196.7	600	422.1–723.7
Time of DM (months)	109.8 ± 96	96	90–120	Not applicable		
IIEF-5 score	12.1 ± 4.6	11	8–17	24.6 ± 0.5	25	24–25

Data are presented as mean ± standard deviation and median (interquartile range).

LDL = low-density lipoprotein; HDL = high-density lipoprotein; BMI = body mass index; HbA1c = glycated hemoglobin; g-LDL = glycated low-density lipoprotein; IIEF-5 = International Index of Erectile Function-5.

Table 2a. Comparison of parameters according to ED severity

Variable	H	p	Effect size (η²)	Post-hoc results
Age	6.53	.089	0.06	–
BMI	8.13	.043	0.09	No significant pairwise difference
LDL	28.83	.001	0.46	G4 > G1, G2, G3
HDL	9.80	.028	0.12	No significant pairwise difference
Triglyceride	42.27	.001	0.70	G4 > G1, G2, G3; G3 > G1
Testosterone	2.37	.499	0.00	–
Glucose	1.21	.751	0.00	–
HbA1c	7.52	.057	0.08	–
g-LDL	24.85	.001	0.39	G4 > G2, G3; G3 > G2
DM duration	28.55	.001	0.46	G4 > G1, G2

Kruskal–Wallis test was used for overall comparisons. Pairwise comparisons were performed using Mann–Whitney U test with Bonferroni correction.

G1: Mild ED; G2: Mild–Moderate ED; G3: Moderate ED; G4: Severe ED.

Table 2b. Distribution of erectile dysfunction severity according to hypertension and smoking status

	Mild n (%)	Mild to moderate n (%)	Moderate n (%)	Severe n (%)	p
Hypertension					
No HT	15 (55.6)	0 (0)	8 (29.6)	4 (14.8)	.017*
HT	7 (21.2)	5 (15.2)	12 (36.4)	9 (27.3)	
Smoking					
Non-smoker	15 (53.6)	4 (14.3)	6 (21.4)	3 (10.7)	.009*
Smoker	7 (21.9)	1 (3.1)	14 (43.8)	10 (31.3)	

Pearson chi-square test, *; significant

Table 3. Ordinal regression analysis of factors associated with erectile dysfunction severity

Variable	B	Std. Error	OR (95% CI)	p
Duration of diabetes	0.040	0.015	1.041 (1.011–1.072)	.008
HbA1c	-0.448	1.474	0.639 (0.036–11.49)	.761
g-LDL	0.014	0.005	1.014 (1.005–1.024)	.003
Smoking	-1.194	0.654	0.303 (0.084–1.093)	.068
Hypertension	-0.158	0.673	0.854 (0.229–3.190)	.814

Results of ordinal logistic regression analysis evaluating independent predictors of erectile dysfunction severity. Odds ratios (OR) with 95% confidence intervals (CI) are presented.

The proportional odds assumption was tested and satisfied ($p > 0.05$).

Table 4. Comparison of biochemical and clinical parameters across study groups

Variable	H	p	Effect size (η^2)	Pairwise comparisons (adjusted p)
g-LDL	90.960	.001	0.76	Control vs Controlled (<0.001) Control vs Uncontrolled (<0.001) Controlled vs Uncontrolled (0.156)
HbA1c	102.105	.001	0.86	Control vs Controlled (<0.001) Control vs Uncontrolled (<0.001) Controlled vs Uncontrolled (0.009)
IIEF	96.161	.001	0.80	Control vs Controlled (<0.001) Control vs Uncontrolled (<0.001) Controlled vs Uncontrolled (0.338)

Comparisons were performed using the Kruskal–Wallis test. Effect sizes were calculated using eta-squared (η^2) based on the Kruskal–Wallis H statistic. Post hoc pairwise comparisons were conducted using the Mann–Whitney U test with Bonferroni correction.

Supplementary Files

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- SupplementaryTableS1.docx