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Serum cathepsin D as a biomarker for vascular atherosclerosis in patients with diabetes mellitus; a case-control study

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ABSTRACT

Introduction: Diabetes mellitus represents a significant global health burden, with affected individuals facing a markedly increased risk of vascular disease. Atherosclerosis, the primary pathological process underlying most cardiovascular events, develops earlier and progresses more rapidly in diabetic patients compared to the general population. The identification of novel biomarkers for early atherosclerosis detection in diabetes remains a critical unmet need in preventive vascular diseases.

Objectives: This study aimed to evaluate the potential utility of cathepsin D as a biomarker for early atherosclerosis detection in diabetic patients.

Patients and Methods: This case-control study, conducted at Ghazi Al-Hariri hospital in Baghdad from February to July 2024, included 100 diabetic patients with vascular atherosclerosis and 50 healthy controls. Demographic and clinical data were collected through interviews and medical records, while blood samples were processed to measure serum cathepsin D and lipid profiles. The study outcomes were assessing the association between cathepsin D levels and the presence and severity of vascular atherosclerosis in diabetic patients, as well as evaluating the diagnostic accuracy of cathepsin D for identifying and stratifying atherosclerotic risk.

Results: The results demonstrated that higher cathepsin D concentrations were significantly associated with increased odds of vascular atherosclerosis in diabetic patients, with an unadjusted and adjusted odds ratio (OR) of 2.08 and 1.71, respectively. In terms of diagnostic utility, cathepsin D showed excellent discriminatory accuracy for identifying vascular atherosclerosis, with an area under the curve (AUC) of 0.940 (95% CI: 0.903–0.978). At a cut-off value of 9.45 ng/mL, cathepsin D achieved a sensitivity of 91% and specificity of 84%. Additionally, cathepsin D levels increased in parallel with the severity of atherosclerosis; diabetic patients at low, moderate, and high risk exhibited progressively higher mean concentrations, with all group differences reaching statistical significance.

Conclusion: In conclusion, the results demonstrated that elevated cathepsin D levels are significantly and independently associated with both the presence and severity of vascular atherosclerosis in diabetic patients. Cathepsin D also shows strong diagnostic accuracy, highlighting its potential as a valuable biomarker for early detection and risk assessment of vascular complications in this population.

Implication for health policy/practice/research/medical education:
This study establishes serum cathepsin D as a clinically relevant biomarker for vascular atherosclerosis in diabetic patients, demonstrating an independent association with atherosclerotic risk and progression. The findings highlight cathepsin D's strong diagnostic accuracy in distinguishing diabetic individuals with atherosclerosis, supported by its capacity to reflect disease severity through stepwise elevation across low-, moderate-, and high-risk subgroups. Clinically, cathepsin D measurement could enhance early atherosclerosis detection in diabetes, enabling timely risk stratification and personalized interventions to mitigate cardiovascular morbidity. While further validation is needed, these results position cathepsin D as both a prognostic tool and a gateway to novel therapeutic approaches in diabetes-related cardiovascular disease (CVD).

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Original Article

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (1). This chronic condition occurs when the body cannot properly regulate blood glucose levels, either because insulin is not being produced at all, is not made at sufficient levels, or is not as effective as it should be (2). The two primary classifications are type 1 diabetes mellitus (T1DM), an autoimmune disorder leading to the destruction of pancreatic beta-cells and affecting approximately 5% of diabetic patients, and type 2 diabetes mellitus (T2DM), which is much more common (90%-95% of cases) and primarily results from progressive impaired glucose regulation due to dysfunctional pancreatic beta cells and insulin resistance (3,4). Other forms include gestational diabetes, maturity-onset diabetes of the young, neonatal diabetes, and secondary causes due to endocrinopathies or steroid use (2,5). The chronic hyperglycemia associated with diabetes is linked to long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels, contributing to its status as one of the leading causes of high mortality and morbidity worldwide (1,6).

Diabetes mellitus drives complex interactions between glomerular vascular dysfunction and cardiovascular disease (CVD), with renal hemodynamic alterations serving as a critical mediator of systemic complications. Glomerular hyperfiltration, characterized by elevated glomerular filtration rate, emerges early in diabetes due to afferent arteriolar vasodilation and impaired renal autoregulation, contributing to both nephropathy and CVD risk (7-9). In type 2 diabetes, Glomerular hyperfiltration is associated with a heightened incidence of myocardial infarction and heart failure, independent of traditional metabolic risk factors, reflecting shared pathways of endothelial dysfunction and inflammation (7,10). Chronic kidney disease, present in ~40% of diabetic patients, exacerbates cardiovascular morbidity by promoting hypertension, fluid overload, and uremic toxin accumulation, while reduced vascular endothelial growth factor A signaling in glomerular podocytes accelerates microvascular injury, further linking renal and cardiac pathology (10,11).

Serum cathepsin D has emerged as a promising biomarker for vascular atherosclerosis in patients with diabetes mellitus, with studies demonstrating its dual role in metabolic dysregulation and vascular injury pathways. Elevated circulating cathepsin D levels correlate strongly with insulin resistance and endothelial dysfunction in type 2 diabetes, key drivers of atherosclerotic plaque formation (12-14). Serum cathepsin D concentrations also showed significant positive associations with carotid intima-media thickness, a direct measure of subclinical atherosclerosis, independent of traditional risk factors (15). Mechanistically, cathepsin D modulates vascular smooth muscle cell (VSMC) behavior under diabetic conditions, where advanced glycation end-products (AGEs) suppress its expression, leading to VSMC proliferation, migration, and senescence, hallmarks of atherosclerotic lesion progression (16). This lysosomal protease also interacts with renal pathophysiology, as evidenced by its urinary elevation preceding rapid glomerular filtration rate decline in type 1 diabetes, creating a bidirectional relationship between diabetic kidney disease and accelerated atherosclerosis through shared inflammatory pathways (17). The biomarker's predictive capacity extends to acute cardiovascular events, where proteomic profiling identifies cathepsin D as the strongest predictor of undetected dysglycemia in myocardial infarction patients, bridging glycemic dysregulation with subsequent atherosclerotic complications (12). These findings position serum cathepsin D as a multifunctional indicator of vascular injury, integrating metabolic, inflammatory, and hemodynamic components of diabetes-associated atherosclerosis, and highlight its potential as a novel biomarker for early detection and risk stratification of vascular atherosclerosis in diabetic patients.

Objectives

This study aimed to evaluate the association between serum cathepsin D concentrations with the presence and severity of vascular atherosclerosis in patients with diabetes mellitus, and to assess the diagnostic utility of cathepsin D as a potential biomarker for identifying and stratifying atherosclerotic risk in this population.

Patients and Methods

Study design and participants

This case-control study was conducted at Ghazi Al-Hariri hospital in Baghdad, Iraq, between February and July 2024, and included 150 diabetic participants, including 100 patients with vascular atherosclerosis and 50 healthy control subjects.

Inclusion and exclusion criteria

Inclusion criteria comprised individuals diagnosed with type 2 diabetes mellitus. Participants without evidence of vascular atherosclerosis were assigned to the control group, while those with documented vascular atherosclerosis, confirmed by initial catheterization, a history of previous catheterization, or having undergone coronary artery bypass graft (CABG) surgery, were allocated to the case group. Exclusion criteria included a history of thyroid disease, immune disorders, and pregnancy.

Data collection

Demographic information, including age, gender, body mass index (BMI), and history of hypertension and smoking, was obtained through participant interviews or extracted from clinical records. For biochemical analysis, five milliliters of venous blood were collected from each participant using a disposable syringe and transferred into vacutainer gel tubes. The samples were allowed to clot at room temperature (25 °C) before being centrifuged at 3000 rpm for five minutes to separate the serum. The isolated serum was then stored at -20 °C until analysis for cathepsin D levels and lipid profile parameters, including cholesterol, triglycerides, High-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c).

Vascular atherosclerosis severity definition

Patients with documented vascular atherosclerosis were stratified according to disease severity: those confirmed by initial catheterization were classified as low risk; individuals with a history of both initial and previous catheterizations were categorized as moderate risk; and patients who had undergone CABG surgery were designated as high risk for vascular atherosclerosis.

Outcomes

This study examined serum cathepsin D's role in vascular atherosclerosis among diabetic patients, with a key focus on its association with atherosclerotic presence. Researchers compared cathepsin D levels between diabetic individuals with confirmed vascular atherosclerosis and diabetic controls without the condition to evaluate this relationship. Additionally, the diagnostic accuracy of cathepsin D was assessed using receiver operating characteristic (ROC) curve analysis, which measured the biomarker's sensitivity, specificity, and area under the curve (AUC) at an optimal threshold. The study further investigated how cathepsin D concentrations correlated with atherosclerosis severity, analyzing gradients across low-, moderate-, and high-risk subgroups to determine its utility in risk stratification.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics (v27). Normality of continuous variables was verified via the Kolmogorov-Smirnov test. Group comparisons utilized independent T-test for normally distributed data and chi-square tests for categorical variables. Logistic regression models (univariate and multivariate) assessed associations between cathepsin D levels and atherosclerosis presence, with results reported as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). The ROC curve analysis determined the optimal diagnostic threshold for cathepsin D, with AUC quantifying discriminatory accuracy. Sensitivity and specificity were calculated at the derived cutoff. Additionally, the relationship between cathepsin D levels and atherosclerosis severity was evaluated using one-way analysis of variance (ANOVA) with post hoc Scheffe test to compare mean concentrations across low-, moderate-, and high-risk subgroups. Statistical significance was defined as $P < 0.05$.

Results

This study consisted of 150 diabetic patients with a mean age of 54.88 ± 8.28 years (50 healthy controls, and 100 patients with vascular atherosclerosis). The results indicated that demographic factors showed no significant difference in gender distribution between groups. However, age, BMI, hypertension status, and smoking history demonstrated a highly significant difference in the frequency distribution between healthy control individuals and vascular atherosclerosis patients. Among clinical parameters, cholesterol, triglyceride, and LDL-c levels were significantly higher in the vascular atherosclerosis patients. The HDL-c levels did not reach statistical significance difference between the two groups. Cathepsin D concentrations showed a strong significant association with vascular atherosclerosis, and its concentration in patients with vascular atherosclerosis was significantly higher than in healthy control individuals (Table 1).

The logistic regression analysis examining the association between cathepsin D levels and vascular atherosclerosis occurrence in diabetic patients demonstrated that both unadjusted and adjusted models demonstrated significant relationships. The unadjusted model revealed that higher cathepsin D concentrations were associated with increased odds of vascular atherosclerosis, with an OR of 2.08, which indicates that for each one ng/mL increase in cathepsin D concentration, the odds of developing vascular atherosclerosis among diabetic patients increase by 2.8 times. After adjusting for potential confounders, including age, gender, BMI, hypertension status, smoking history, cholesterol, triglyceride, HDL-c, and LDL-c levels, the association remained significant, though slightly attenuated, with an OR of 1.71. These findings suggest that elevated cathepsin D levels are independently associated with a higher occurrence of vascular atherosclerosis in diabetic patients (Table 2).

Table 3 and Figure 1 present the diagnostic value of cathepsin D levels for identifying vascular atherosclerosis in diabetic patients. The cathepsin D concentration demonstrated significant diagnostic utility in identifying vascular atherosclerosis among diabetic patients, as evidenced by an AUC of 0.940 (95% CI: 0.903–0.978), indicating high discriminatory accuracy. At a cut-off value of 9.45 ng/mL, cathepsin D achieves 91% sensitivity and

Table 1. Frequency distribution of demographic and clinical data among healthy individuals and patients with vascular atherosclerosis

Variable	Sub-variable	Healthy control individuals (n = 50)		Vascular atherosclerosis (n = 100)		*P* value
		No.	%	No.	%	
Gender	Female (n = 59)	23	39	36	61	0.237*
	Male (n = 91)	27	29.7	64	70.3	
Hypertension	No (n = 78)	47	60.3	31	39.7	<0.001*
	Yes (n = 72)	3	4.2	69	95.8	
Smoking	No (n = 85)	41	48.2	44	51.8	<0.001*
	Yes (n = 65)	9	13.8	56	86.2	
Variable	**Sub-variable**	**Mean**	**SD**	**Mean**	**SD**	***P* value**
Age (year)		46.96	7.11	57.49	7.29	<0.001*
BMI (kg/m^2)		27.53	3.51	28.90	3.62	0.029*
Cholesterol (mg/dL)		166.02	12.34	199.38	42.12	<0.001*
Triglyceride (mg/dL)		133.94	17.19	166.54	51.62	<0.001*
HDL-c (mg/dL)		43.34	7.56	39.18	20.53	0.075*
LDL-c (mg/dL)		95.01	8.63	124.82	40.49	<0.001*
Cathepsin D (ng/mL)		7.76	1.89	14.73	4.05	<0.001*

SD: Standard deviation; BMI: Body mass index; LDL-c: Low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol. *Chi-square, **Independent T-test.

Table 2. The association of cathepsin D levels with vascular atherosclerosis incidence using logistic regression in diabetic patients

Biomarker		Vascular atherosclerosis incidence			
		P value	OR	95% CI	
				Lower	Upper
Cathepsin D (ng/mL)	Unadjusted	<0.001	2.08	1.60	2.71
	Adjusted	0.004	1.71	1.19	2.47

OR: Odds ratio; CI: Confidence interval.

84% specificity, reflecting its robust capacity to balance true-positive identification while minimizing false-positive results (Table 3 and Figure 1).

An analysis of the relationship between cathepsin D concentrations and the severity of vascular atherosclerosis in diabetic patients reveals a clear trend: as the severity of atherosclerosis increases, cathepsin D levels also rise. Healthy individuals exhibit the lowest cathepsin D concentrations, while diabetic patients with low, moderate, and high risk of vascular atherosclerosis display progressively higher levels. Statistical comparisons indicate that each step up in atherosclerosis risk category is associated with a significant increase in cathepsin D, with the differences between all groups being statistically significant. These findings suggest a strong positive correlation between cathepsin D levels and the severity of vascular atherosclerosis in diabetic patients, highlighting the potential of cathepsin D as a biomarker for vascular risk stratification in this population (Table 4).

Discussion

Our study found that elevated serum cathepsin D levels were strongly linked to vascular atherosclerosis risk in diabetic patients, showing unadjusted and adjusted odds ratios of 2.08 and 1.71, respectively. The biomarker exhibited outstanding diagnostic performance for atherosclerosis detection, achieving an AUC of 0.940. At the optimal threshold of 9.45 ng/mL, it demonstrated high clinical utility with 91% sensitivity (identifying true positives) and 84% specificity (excluding false

Table 3. Diagnostic value of cathepsin D levels in the diagnosis of vascular atherosclerosis incidence in diabetic patients

Biomarker	Vitamin D diagnostic value						
	AUC (0-1)	*P* value	95% CI		Cut off (ng/mL)	Sensitivity (%)	Specificity (%)
			Lower	Upper			
Cathepsin D (ng/mL)	0.940	<0.001	0.903	0.978	9.45	91	84

AUC: Area under curve; CI: Confidence interval.

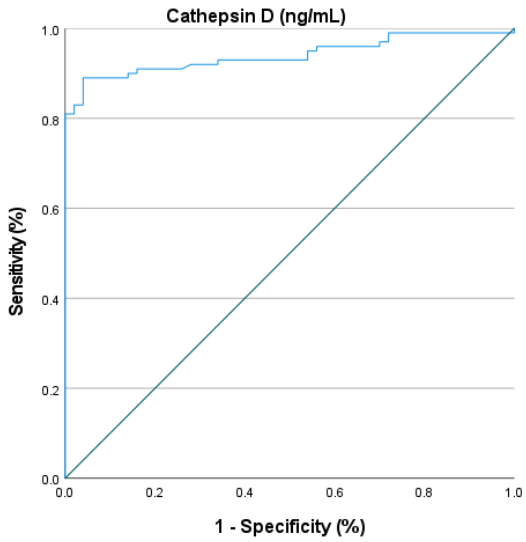

Figure 1. Diagnostic value of cathepsin D levels in predicting vascular atherosclerosis incidence using ROC curve analysis.

positives). The current findings demonstrating elevated serum cathepsin D levels as a robust predictor of vascular atherosclerosis in diabetic patients align with prior evidence linking this lysosomal protease to diabetic vascular pathophysiology. A study by Liu et al demonstrated that circulating cathepsin D concentrations are significantly higher in newly diagnosed type 2 diabetes compared to controls, correlating with insulin resistance and cardiac dysfunction, which are key drivers of atherosclerosis (14). The recent study conducted by Gonçalves et al revealed a significant correlation between the levels of cathepsin D present in the body and the likelihood of developing coronary artery atherosclerosis. Specifically, the researchers observed that individuals with elevated concentrations of cathepsin D were at a greater risk of experiencing this particular form of CVD, which involves the hardening and narrowing of the arteries supplying blood to the heart (18). The diagnostic accuracy reported here (AUC 0.940) surpasses earlier observations in chronic kidney disease cohorts in a study by Ozkayar et al, where cathepsin D predicted endothelial dysfunction with 80% sensitivity and 60% specificity at a higher cutoff, reinforcing its association with atherosclerosis severity (13). Notably, the strong predictive capacity of cathepsin D for undetected dysglycemia in myocardial infarction patients (12) further bridges metabolic dysregulation and atherosclerotic risk, highlighting its dual role in glycemic and vascular pathways. However, contrasting mechanistic studies suggest context-dependent roles, as cathepsin D overexpression in VSMCs inhibits AGE-induced proliferation and migration (16), implying potential protective effects at the cellular level. This paradox may reflect differential tissue-specific actions or compensatory mechanisms in advanced disease. Collectively, the evidence positions serum cathepsin D as a multifunctional biomarker integrating metabolic, inflammatory, and hemodynamic components of diabetes-associated atherosclerosis, though standardization of assays and validation in diverse cohorts are needed to translate these findings into clinical practice.

Furthermore, the concentration of cathepsin D was found to be elevated in direct relation to the degree of atherosclerotic plaque burden. This means that as the condition of atherosclerosis worsened, the levels of cathepsin D also rose correspondingly. Specifically, when examining diabetic patients stratified by their risk for cardiovascular events, those in the low-risk category demonstrated the lowest mean cathepsin D concentrations, while those considered to be at moderate risk exhibited higher mean concentrations. Finally, individuals classified as high-risk patients displayed the highest mean cathepsin D concentrations of all three groups. The observed correlation between elevated serum cathepsin D levels and atherosclerotic plaque burden aligns with prior clinical studies underscoring its role in vascular pathology. Cathepsin D's capacity to modify LDL-c into aggregated

Table 4. The correlation between cathepsin D level and the severity of vascular atherosclerosis in diabetic patients

Vascular atherosclerosis severity		Cathepsin D (ng/mL)		*P* value*
		Mean	SD	
Healthy control individuals (n = 50)		7.76	1.89	<0.001
Low risk (n = 26)		12.59	2.04	
Moderate risk (n = 59)		15.05	3.97	
High risk (n = 15)		17.15	5.27	
Atherosclerosis severity classification		**Mean difference**	**Std. error**	***P* value****
Healthy control	Low risk	4.82	0.79	<0.001
	Moderate risk	7.29	0.63	<0.001
	High risk	9.38	0.97	<0.001
Low risk	Moderate risk	2.46	0.77	0.021
	High risk	4.56	1.06	<0.001
Moderate risk	High risk	2.09	0.95	0.030

SD: Standard deviation. *One-way ANOVA, **Post hoc Scheffe test.

forms that promote macrophage uptake and foam cell formation provides a direct biochemical link to plaque development (18,19). The protease's dual role in both metabolic dysregulation and vascular injury is further highlighted by its association with insulin resistance in type 2 diabetes (14), a population at heightened atherosclerotic risk. However, contrasting data exist: while cathepsin D overexpression in VSMCs inhibited AGE-induced proliferation and migration, suggesting a protective role against plaque instability (16), its extracellular release in atherosclerotic lesions promotes macrophage apoptosis and matrix degradation, exacerbating plaque vulnerability (18,19). This paradox may reflect tissue-specific actions, where intracellular cathepsin D in VSMCs maintains vascular homeostasis, while its extracellular leakage from macrophages or lysosomal dysfunction in diabetes amplifies inflammatory cascades. Notably, the current findings extend earlier proteomic analyses identifying cathepsin D as a predictor of undetected dysglycemia in myocardial infarction patients (16), bridging glycemic dysfunction with atherosclerotic progression. Collectively, cathepsin D emerges as a multifaceted biomarker reflecting both metabolic stress and vascular remodeling in atherosclerosis, though its context-dependent roles necessitate further mechanistic clarification to harness its therapeutic potential.

Conclusion

In conclusion, the results of this study demonstrate that cathepsin D is strongly and independently associated with both the presence and severity of vascular atherosclerosis in diabetic patients. Elevated cathepsin D levels not only increase the odds of developing vascular atherosclerosis, even after adjusting for traditional cardiovascular risk factors, but also correlate closely with the progression of disease severity. Furthermore, cathepsin D exhibits excellent diagnostic accuracy, with high sensitivity and specificity at an optimal threshold, underscoring its potential utility as a reliable biomarker for early detection and risk stratification of vascular atherosclerosis in the diabetic population. These findings suggest that incorporating cathepsin D measurement into clinical practice may enhance the identification and management of diabetic patients at risk for vascular complications, ultimately contributing to improved cardiovascular outcomes.

Limitations of the study

The single-center recruitment in Baghdad may limit generalizability to other populations, particularly given potential regional differences in genetic, environmental, or lifestyle factors influencing diabetic vascular complications. Atherosclerosis severity was stratified using clinical interventions (catheterization/CABG), but the absence of advanced imaging metrics like coronary artery calcium scoring or intravascular ultrasound may oversimplify risk categorization. The residual confounding from unmeasured variables, such as physical activity, dietary patterns, or genetic predispositions, could influence observed associations. The reliance on self-reported smoking history and medical records introduces potential recall and documentation biases.

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Authors' contribution

Conceptualization: Israa Saad Salim and Walaa Esmail Jasim.
Data curation: Israa Saad Salim and Ahmed Saadi Hassan.
Formal analysis: Ahmed Saadi Hassan.
Investigation: Israa Saad Salim and Walaa Esmail Jasim.
Methodology: Walaa Esmail Jasim and Ahmed Saadi Hassan.
Project Management: Israa Saad Salim.
Resources: All authors.
Supervision: Walaa Esmail Jasim.
Validation: Ahmed Saadi Hassan.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI (Perplexity.ai and Grammarly.com) to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

The research was conducted in accordance with the principles of the Declaration of Helsinki. Informed written consent was obtained from all participants. This research resulted from a medical laboratory student thesis by Israa Saad Salim, registered under thesis number

9904 on March 6, 2024. It was approved by the Ethics Committee of the Department of Medical Teaching at the Iraqi Ministry of Health, College of Health and Medical Technology, Middle Technical University, Baghdad, Iraq. Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

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