Cathepsin D and Its Relation with Lipid Profile in Coronary Atherosclerosis Patients

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كاثبسين D وعلاقته بالدهون في مرضى تصلب الشريان التاجي

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Abstract

Background: Coronary atherosclerosis is a long lasting and continuously evolving disease with multiple clinical manifestations ranging from asymptomatic to stable angina, acute coronary syndrome (ACS), heart failure (HF) and sudden cardiac death (SCD). The onset and advancement of coronary atherosclerosis are influenced by both genetic and environmental factors. **Objectives**: The study aimed to find out if cathepsin D a good indicator to diagnose atherosclerosis and cardiovascular diseases and its relation with lipid profile. **Materials and Methods**: The study conducted with the participation of 150 subjects (100 patients with coronary atherosclerosis and 50 healthy control). Age for all subject was in range 40-70 years. All participants were subjected for laboratory measurement of cathepsin D level by Enzyme-Linked Immunosorbent Assay (ELISA), and lipid profile parameters by using manual kits. **Results**: There are significant elevation in the levels of both cathepsin D (P = <0.001) and all lipid profile parameters (P = <0.001), except for high density lipoprotein in patients with coronary atherosclerosis. **Conclusion**: Cathepsin D can be used as a good indicator for detecting coronary atherosclerosis along with high levels of lipid profile parameters (and low levels of high density lipoprotein) in comparison to healthy control.

Keywords: Coronary atherosclerosis, Cathepsin D, Lipid profile, Catheterization, Cardiovascular diseases.

المستخلص

الخلفية: تصلب الشرايين التاجي هو مرض طويل الامد ومتطور باستمرار مع مظاهر سريرية متعددة تمتد من عدم وجود اعراض الى الذبحة الصدرية المستقرة، متلازمة الشريان التاجي الحادة، فشل القلب، والموت القلبي المفاجئ. يتأثر ظهور وتطور تصلب الشرايين التاجي بالعوامل الوراثية والبيئية على حدٍ سواء. **الاهداف**: هدفت الدراسة الى معرفة ما اذا كان الكاثبسين D مؤشراً جيداً لتشخيص تصلب الشرايين وأمراض القلب والاوعية الدموية وعلاقته بالدهون. **المواد والطرق**: أُجريت الدراسة بمشاركة 150 شخصاً (100 مريض يعانون من تصلب الشرايين التاجي و50 شخصاً اصحاء). كان العمر لجميع الاشخاص يتراوح بين 40 و 70 سنة. تم اخضاع جميع المشاركين للقياس المختبري لمستوى الكاثبسين D عن طريق الفحص المناعي المرتبط بالانزيم (ELISA)، ومُعلمات الدهون باستخدام الطرق اليدوية.

النتائج: هناك ارتفاع معنوي في مستويات كل من الكاثبسين D ($P = <0.001$) وجميع مُعلمات الدهون ($P = <0.001$)، باستثناء البروتين الدهني عالي الكثافة في المرضى الذين يعانون من تصلب الشرايين التاجي. **الخلاصة**: يُمكن استخدام الكاثبسين D كمؤشر جيد للكشف عن تصلب الشرايين التاجي الى جانب المستويات المرتفعة من مُعلمات الدهون (ومستويات منخفضة من البروتين الدهني عالي الكثافة) مقارنةً بالأشخاص الاصحاء.

الكلمات المفتاحية: تصلب الشرايين التاجي، الكاثبسين D، الدهون، القسطرة، أمراض القلب والأوعية الدموية.

1. Introduction

Cardiovascular diseases (CVDs) are one of the leading causes of mortality worldwide and significantly lower life quality (Harikrishnan *et al.*, 2018).

Atherosclerosis considered the root cause for many forms of CVDs. The term atherosclerosis derives from the Greek "athere" (gruel) and "skleros" (hard), which describes the waxy plaques inside blood arteries. This condition is well known to progress gradually for decades without causing any notable signs until the patient encounters serious complications. Hypertension, diabetes mellitus, hypercholesterolemia, obesity, and smoking are risk factors for atherosclerosis (Libby *et al.*, 2019). Hypercholesterolemia has been identified as the greatest attributable risk factor for atherosclerosis and subsequent coronary heart disease (CHD). Furthermore, it was demonstrated that progression from early-stage fatty streaks to advanced-stage, lipid-rich lesions was directly linked to continuous high levels of low density lipoprotein-cholesterol (LDL-C) (Nicholas *et al.*, 2019). Lysosomes are small cytoplasmic organelles containing a variety of acidic hydrolytic enzymes that are capable of degrading different biological polymers, such as proteins, lipids, carbohydrates, and nucleic acids (Ballabio and Bonifacino, 2020). Lysosomal cathepsins were shown to be implicated in the etiology of CVDs (Liu *et al.*, 2018). Cathepsin D (CatD) is a ubiquitous, lysosomal, aspartic endo-proteinase, which synthesized in rough endoplasmic reticulum, and proteolytically active in acidic pH. CatD is mostly released following oxidative stress, and it is essential for protein degradation, proteolytic activation of hormones and growth factors (Mijanovic *et al.*, 2021). Clinical observations have indicated a possible substantial involvement of cathepsin D (CatD) derangement in cardiovascular pathophysiology (Imanaka *et al.*, 2020). This study aimed to find out if cathepsin D is a good indicator to diagnose atherosclerosis and cardiovascular diseases and its relation with lipid profile.

2. Materials and Methods

2.1. Patients and samples

This study comprised 150 participants, distributed into two groups, 100 patients (64 males and 36 females), and 50 healthy controls (26 males and 24 females). The ages of both groups are ranging from 40 to 70 years. Patients` samples of the study were collected in Iraqi Center of Heart Diseases in Ghazi Al-Hariri hospital in Baghdad city, while control samples were collected from medical staff and special laboratory during the time period from February to July, 2024.

2.2. Evaluations of CatD and lipid profile serum level

Serum CatD level was evaluated using Enzyme-Linked Immunosorbent Assay (ELISA), and lipid profile parameters by using manual kits.

2.3. Ethical approval

The ethical committees of the Middle Technical University, College of Health and Medical Techniques gave their approval for the study.

2.4. Statistical analyses

The data were analyzed using SPSS (V.20, IBM). The T-test and One Way ANOVA test were used as appropriate tests. One Way ANOVA test was used by obtaining least significant difference (LSD) to find p value between the studied groups. The data were presented as Mean ± S.E. and the p value ≤ 0.05 was considered as significant result. In addition, Pearson Correlation

Coefficient (r) was used to find the correlation between the studied parameters. ROC test also was performed for parameters to find AUC, sensitivity, and specificity of each studied parameter.

3. Results

3.1. Lipid profile levels in studied groups

Data illustrated in Table (1) showed that there is an increasing in the levels of lipid profile parameters, which include cholesterol, triglyceride, high density lipoprotein (HDL), LDL, and very low density lipoprotein (VLDL), in patients with atherosclerosis in contrast to control. Since the p value was highly significant (P-value <0.001), there was a significant difference between patients and control group in levels of lipid profile.

Table (1): Comparison between the levels of lipid profile parameters among patients and control

Parameter	Groups	Concentration (Mean ± S.E.)	P value
Cholesterol	Control	166±1.75	<0.001**
	Patients	199.38±4.21	
Triglyceride	Control	129.72±2.37	<0.001**
	Patients	183.55±6.57	
HDL	Control	43.34±1.07	0.008**
	Patients	37.84±1.76	
LDL	Control	94.51±1.27	<0.001**
	Patients	141.39±3.15	
VLDL	Control	27.25±0.56	<0.001**
	Patients	36.30±1.43	

**** Highly significant P value**

3.2. Cathepsin D level in studied groups

Table (2) showed an increase in the level of CatD in patients with atherosclerosis. There was a significant difference between patients and control group in level of CatD due to highly significant P value (<0.001).

Table (2): Comparison between the level of CatD among patients and control

Parameter	Groups	Concentration (Mean ± S.E.)	P value
Cathepsin D	Control	7.77±0.27	<0.001**
	Patients	15.32±0.35	

**** Highly significant P value**

3.3. Comparison of CatD level between control and different groups of patients

As showed in Table (3), Patients were divided into 3 groups: first catheterization, previous catheterization, and cardiovascular (CV) transplantation. There was increasing in the level of CatD among patients groups compared to control. Also, there were significant differences between control and the three patients groups (P value <0.001), and the significant difference is also seen between patients groups (previous catheterization and CV transplantation) compared to first catheterization group (P value <0.001).

Table (3): Comparison of CatD between control and different groups of patients

Parameter	Patients groups	Concentration (Mean ± S.E.)	P value
Cathepsin D	Control	7.77±0.27	<0.001**
	First catheterization	12.59±0.40 b	<0.001**
	Previous catheterization	16.08±0.38 b	
	CV transplantation	16.77±0.99 b	

**** Highly significant P value, b vs. First catheterization**

3.4. Comparison of lipid profile levels between control and different patients groups according to blood pressure

In Table (4), blood pressure patients are divided into 2 categories, those with high blood pressure (yes), and those with normal blood pressure (no). All control subjects are normal. Significant differences were found in the level of cholesterol between control and patients categories (P value <0.001), and these differences especially found in patients with high and normal blood pressure within first catheterization and CV transplantation groups, and also in patients with high blood pressure within previous catheterization group compared to control. However, insignificant differences were noticed between blood pressure categories and patients groups. For the level of triglyceride, significant differences between control and blood pressure categories were demonstrated (P value <0.001), especially in patients with high blood pressure within first catheterization group, and in blood pressure categories within both previous catheterization and CV transplantation groups in comparison to control. Although that, there were non-significant differences in blood pressure categories within both first and previous catheterization groups. In contrast, there was a significant difference between blood pressure categories and CV transplantation group (P value ≤0.05). In addition, significant differences were observed in the level of HDL between control and blood pressure categories (P value ≤0.05), mostly in patients with normal blood pressure within first catheterization and CV transplantation groups, and in patients with high blood pressure within previous catheterization group in comparison to control. Insignificant differences were found in blood pressure categories within both first and previous catheterization groups. Additionally, there were significant differences between blood pressure categories and CV transplantation group (P value ≤0.05).

For the level of LDL, significant differences were found between control and blood pressure categories (P value <0.001). In comparison to control, these differences were observed especially in all patients who have normal and high blood pressure within all patients groups. Non-significant differences were noticed between blood pressure categories and both first and previous catheterization groups. In contrast, there was significant difference between blood pressure categories and CV transplantation group (P value ≤0.05). For the level of VLDL, there were significant differences between control and blood pressure categories (P value <0.001), particularly in patients with high blood pressure within first catheterization group, and in both patients categories who have normal and high blood pressure within previous catheterization and CV transplantation groups compared to control. Non-significant differences were demonstrated in blood pressure categories within both first and previous catheterization groups. Although that, there was significant difference between blood pressure categories and CV transplantation group (P value ≤0.05).

Table (4): Comparison of lipid profile levels between control and patients' groups according to blood pressure

Parameter	Groups	Blood pressure categories	Concentration (Mean ± S.E.)	P value
Cholesterol	Control	NO (50)	166±1.75	<0.001**
	First catheterization	NO (12)	208.25±14.25 a	0.16 NS
		Yes (14)	188.79±9.40 a	
	Previous catheterization	NO (10)	189.50±16.30	0.42 NS
		Yes (42)	199.64±4.78 a	
	CV transplantation	NO (8)	205.38±23.21 a	0.9 NS
		Yes (14)	205.21±13.89 a	
Triglyceride	Control	NO	129.72±2.37	<0.001**
	First catheterization	NO	152.00±7.59	0.09 NS
		Yes	187.29±18.39 a	
	Previous catheterization	NO	204.00±19.83 a	0.1 NS
		Yes	174.40±6.75 a	
	CV transplantation	NO	242.25±55.61 a	0.017*
		Yes	186.14±11.36 a	
HDL	Control	NO	43.34±1.07	0.05*
	First catheterization	NO	33.83±3.81 a	0.087 NS
		Yes	43.93±7.69	
	Previous catheterization	NO	36.30±2.31	0.99 NS
		Yes	36.21±1.98 a	
	CV transplantation	NO	31.50±3.12 a	0.046*
		Yes	44.79±6.81	
LDL	Control	NO	94.51±1.27	<0.001**
	First catheterization	NO	147.73±13.94 a	0.2 NS
		Yes	134.33±8.63 a	
	Previous catheterization	NO	137.42±12.12 a	0.8 NS
		Yes	139.58±3.88 a	
	CV transplantation	NO	162.48±8.24 a	0.04*
		Yes	139.23±7.70 a	

*** Significant P value, ** Highly significant P value, NS. Non-significant P value, a vs. control (NO)**

3.5- Comparison of CatD level between control and patients groups according to blood pressure

Table (5) showed a significant difference between control and blood pressure categories (P value <0.001). In comparison to control, these differences were mostly demonstrated in all patients who have high and normal within the three patients groups. In contrast, there were non- significant differences between blood pressure categories and any patient group.

Table (5): Comparison of CatD level between control and patients groups according to blood pressure

Parameter	Groups	Blood pressure categories	Concentration (Mean ± S.E.)	P value
Cathepsin D	Control	NO	7.77±0.27	<0.001**
	First catheterization	NO	13.07±0.65 a	0.42 NS
		Yes	12.18±0.49 a	
	Previous catheterization	NO	15.54±0.60 a	0.5 NS
		Yes	16.21±0.44 a	
	CV transplantation	NO	15.89±1.51 a	0.3 NS
		Yes	17.26±1.32 a	

**** Highly significant P value, NS. Non-significant P value, a vs. control (NO)**

3.6. ROC curve for Cathepsin D

Receiver operating characteristic (ROC) curve is used for determining the existence or absence of a disease. ROC goal is to categorize disease condition as either positive or negative based on test results, and to detect the ideal cut-off value with the optimum diagnostic performance. Sensitivity is the percentage of people who actually have a target disease that are tested positive, while specificity is the percentage of people who actually do not have a target disease that are tested negative. The ideal test would have a sensitivity and specificity equal to 1.0 (Joo *et al*., 2020). The area under curve (AUC) is primarily used to measure the accuracy of a diagnostic test. The closer the ROC curve is to the upper left corner of the graph, the higher the accuracy of the test as Nahm (Nahm, 2022) mentioned it, Furthermore, Fig. 1 illustrated this explanation.

Table (6) showed statistics of CatD. According to this study, AUC for CatD was 0.98, cutoff value was 10.123, the sensitivity of CatD was 95%, and specificity was 96%, with highly significant P value (<0.001). These findings suggest that CatD is very good indicator for detecting and predicting the presence of atherosclerosis. Further researches on cathepsin D are required to determine more pathological characteristics such as degree of disease progression and complications.

Table (6): ROC curve for Cathepsin D

AUC	cutoff	Sensitivity	Specificity	P Value
0.98	10.123	95%	96%	<0.001**

**** Highly significant P value (< 0.001)**

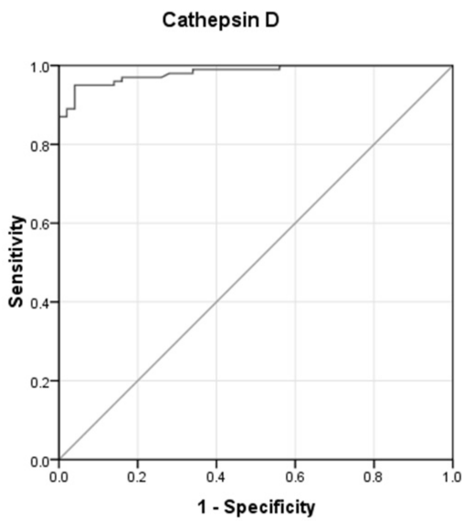

Figure (1): ROC curve of cathepsin D

4. Discussion

Findings obtained by this research agree with a study concerned with abnormal levels of lipid profile and obesity associated with coronary artery diseases (CADs) in Pakistani subjects. The study revealed the occurrence of hyperlipidemia in all cases for all lipid parameters except for HDL, which is decreased, and this can elevate predisposition to complications (Shabana *et al.*, 2020). Elevated levels of serum CatD were associated with endothelial dysfunction, atherogenesis, increased risk of coronary events, and carotid intima-media thickness (Gonçalves *et al.*, 2016). It was found in a previous studies that CatD concentrations were significantly higher in the CADs compared with healthy control, and this agrees with data displayed in the table (Amir *et al.*, 2018). Moreover, increased CatD activation has been found in patients with cardiovascular events (Liu *et al.*, 2017). This study is the first that address the relationship of CatD levels with the progression and development of atherosclerosis in Iraq.

Epidemiological studies showed that elevated blood cholesterol level was associated with atherosclerotic cardiovascular diseases (ASCVDs) (Robinson *et al.*, 2018). Multiple clinical researches showed that number, size, and alterations in LDL can determine initiation and progression of atherosclerosis (Vekic *et al.*, 2022). The study showed that the values of HDL in control group was higher than the values in patients' groups. This findings lead to the belief that HDL may have an atheroprotective characteristics, and two recent MR studies found an independent association between HDL levels and CADs (Zhao *et al.*, 2021). According to the American Association for Clinical chemistry, a normal VLDL level is up to 30mg\dl. Measurements above this point indicate high VLDL levels which raise the risk of heart disease and stroke (Kuti *et al*., 2024). Two of the main causes of heart disease are high blood pressure and high cholesterol. When arteries become tight and restricted from deposited cholesterol, the heart needs to work hard to push blood through them. Consequently, blood pressure continually rises (Hui *et al.*, 2023). Elevated triglycerides frequently indicate other conditions that raise the risk of heart disease and stroke, such as obesity and metabolic syndrome (Shimizu *et al.*, 2015). On the other hand, the composition and function of HDL are changed by elevated blood pressure. However, it is unclear exactly how HDL contributes to the cardiovascular problems associated with hypertension (Aishah & Fawzi, 2022).

In a case-control study conducted in Jakarta, it was found that correlation between dyslipidemia and CHD varied according to hypertensive state. It was noticed that dyslipidemic individuals have an 18-fold higher risk of CHD incidence if they have a hypertension or a history of hypertension compared to those who are non-dyslipidemic. Whereas in dyslipidemic individuals who are not hypertensive or have no history of hypertension, it was found that there is 2.5-fold higher risk of developing CHD than non-dyslipidemic individuals. Dyslipidemia considered a predictor for CHD, and has a role in process of atherogenesis (Ariyanti & Besral, 2019).

5. Conclusion

At the end of this study, it was demonstrated that patients with atherosclerosis have higher levels of lipid profile parameters in comparison to healthy control, except for HDL levels, which have decreased levels in patients. This is due to possibility that some HDL particles have athero-protective ability. In addition, atherosclerosis patients have increased levels of circulating CatD levels compared to control. The study revealed high sensitivity (95%) and specificity (96%) for CatD, making it a very good indicator for detecting and predicting the presence of atherosclerosis.

6. Recommendations

We recommended a study that addresses other types of cathepsins, like cathepsin A, B, and E, and their relationships with coronary atherosclerosis and comparing the results with this study to deduce the most predictive types of cathepsins for the disease.

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