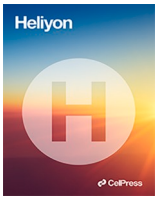
Heliyon 10 (2024) e37777

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Association of plasma endothelin-1 levels with revascularization strategies and short-term clinical outcomes: Role of diabetes

Fadia Mayyas [a,*], Khalid Ibrahim [b], Rasheed Ibdah [c], Abdullah Al-Kasasbeh [c], Muhannad J. Ababneh [c], Ala'Eldin A. Ababneh [c], Mohammad I. Jarrah [c], Sukaina Rawashdeh [c]

[a] Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan
[b] Division of Cardiac Surgery, Department of General Surgery, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan
[c] Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan

ARTICLE INFO

Keywords:
Diabetes mellitus
Coronary artery disease
Cardiovascular event
Cerebrovascular event
Endothelin-1
Revascularization
Percutaneous coronary intervention
Coronary artery bypass surgery

ABSTRACT

Mortality rate due to coronary artery disease (CAD) is elevated among diabetes mellitus (DM) compared to non-DM patients. Endothelin 1 (ET-1), a potent vasoconstrictor, is implicated in the pathophysiology of both CAD and DM. The impact of ET-1 on the short-term clinical outcomes following revascularization by percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) remains unclear. We investigated the impact of ET-1 on clinical outcomes and revascularization strategies in CAD patients, exploring the role of DM on modifying these relationships. In a prospective observational study, patients presenting to cardiac catheterization lab for CAD evaluation at a Jordanian hospital were enrolled and stratified by status of CAD and DM. Plasma levels of ET-1 were measured before catheterization. Short-term clinical outcomes and prognosis were compared.

Among 815 enrolled patients (603 CAD and 212 controls), DM prevalence was higher among CAD patients than non-CAD. Plasma ET-1 levels were measured in 490 random patients and were associated with CAD and the need for revascularization. Multivariate analysis independently revealed higher plasma ET-1 levels in DM patients requiring revascularization. Short-term follow-up for 366 patients (median of 4 months) showed that 132 developed one cerebro/cardiovascular event, predominantly among DM patients. Baseline ET-1 was not associated with higher risk of the first event. Notably, revascularization by PCI was associated with lower event risk in DM patients.

Our study indicates that plasma ET-1 levels are associated with the need for revascularization in DM patients, with those undergoing PCI having a lower risk of initial cerebro/cardiovascular events.

1. Introduction

Diabetes Mellitus (DM) is a common disease linked to cardiovascular complications, with atherosclerosis being the primary cause of

* Corresponding author. Department of Clinical Pharmacy/Faculty of Pharmacy Jordan University of Science and Technology, 3030 Irbid, 22110, Jordan.
E-mail address: famayyas@just.edu.jo (F. Mayyas).

https://doi.org/10.1016/j.heliyon.2024.e37777
Received 4 November 2023; Received in revised form 23 July 2024; Accepted 10 September 2024
Available online 11 September 2024

morbidity and mortality among DM patients. Mortality rates due to coronary artery disease (CAD) and stroke are 2–4 times higher in DM patients compared to non-DM patients [1]. Disturbances in vascular homeostasis arising from smooth muscle and endothelial dysfunction contribute to vasculopathy in DM, fostering a pro-inflammatory and thrombotic state conductive to thrombosis [2].

Hyperglycemia and insulin resistance promote endothelial dysfunction in DM, characterized by reduced nitric oxide (NO) and elevated endothelin-1 (ET-1) and angiotensin II levels, which intensify vascular resistance and smooth muscle cell proliferation and migration [1]. ET-1 is a potent vasoconstrictor, mitogen, and promoter of cardiac and vascular inflammation. We have previously shown that plasma ET-1 levels are elevated in CAD patients and are associated with myocardial infarction (MI), heart failure (HF), and low left ventricular ejection fraction [3]. Plasma ET-1 levels have been reported to rise in DM patients [4]. Increased circulating ET-1 was recently found associated with mortality in patients with stable CAD [5].

Interestingly, high plasma levels of big ET-1 have been found associated with an increased risk of adverse cardiovascular outcomes in patients with coronary in-stent restenosis and DM [6].

Severe CAD patients may need revascularization procedures to reduce ischemic complications and improve quality of life and outcomes. These procedures include percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) [7,8]. The selection of the appropriate revascularization option in DM patients should consider the overall burden of CAD, which highly influences clinical prognosis. The presence of DM worsens both early and late outcomes of acute coronary syndrome (ACS). In addition, long-term outcomes after revascularization strategies (PCI and CABG) are worse for patients requiring insulin [8]. It remains unclear whether plasma ET-1 influences the selection of coronary revascularization and how ET-1 effect may be modified by the presence of DM.

In the present study, we evaluated the association of plasma ET-1 with the choice of revascularization and short-term clinical outcomes, and whether DM status modifies the impact of ET-1. We hypothesized that high plasma ET-1 level is associated with the need for revascularization by PCI/CABG, and this association is more evident among DM patients. Our study may identify potential biological predictors for revascularization in DM patients and aid in developing potential target therapies to reduce CAD development or progression.

2. Methods

2.1. Study population

This is a prospective observational cohort study evaluating the impact of baseline plasma ET-1 levels on the need for revascularization and follow-up clinical outcomes, with a focus on the role of DM. The inclusion criteria were consecutive patients at King Abdullah University Hospital (KAUH) between February 2020 and October 2021, presenting with underlying angina-like symptoms requiring coronary angiography for appropriate diagnosis, and, if indicated, reperfusion by PCI or CABG. This study followed STROBE guidelines.

Exclusion criteria included patients with inflammatory disease, recent infection, recent surgery or trauma, and cancer. These conditions were excluded as they may acutely increase plasma ET-1 and confound the results of the study.

CAD was confirmed by $\geq$ 50 % stenosis in one or more of the main coronary arteries. CAD patients were further classified as stable angina, unstable angina, and myocardial infarction (MI). Patients with non-significant CAD (<50 % stenosis) and no evidence of MI served as controls. Patients were subclassified into DM and non-DM patients.

2.2. Assessmnet

Detailed history, physical examinations, and relevant laboratory tests were used to establish DM and MI diagnosis. DM criteria included fasting plasma glucose (FPG) $\geq$ 126 mg/dl ($\geq$7 mmol/L) and/or glycated hemoglobin (HbA1c) $\geq$ 6.5 % ($\geq$48 mmol/mol). Patients with a prior history of DM were included, and DM was documented by diagnostic lab tests (FPG and HbA1c) and antidiabetic drug use. Clinical characteristics, disease progression, diabetes autoantibody panel, and C-peptide or insulin assay tests were used to distinguish type 1 and type 2 DM. Angina was defined as chest pain at rest (unstable angina) or during exertion (stable angina) with slight or marked limitation of ordinary physical activity without enzyme leak. MI was established as presence of angina lasting >20min, characteristic ECG changes, and elevated plasma cardiac enzyme concentrations.

Approval from the Institutional Review Board of KAUH (IRB # 20/130/2020, Date January 30, 2020) was obtained, and was conducted according to the principles of the Declaration of Helsinki as revised in 2013. Written informed consent was collected from patients.

A comprehensive clinical data sheet was prepared for each patient, detailing demographics, clinical characteristics, and medication use. Data were acquired from patients' electronic data systems and paper files at the cardiology outpatient clinic of KAUH.

Patients with CAD were evaluated by the cardiology team to receive standard medical therapy, PCI, or CABG according to standard guidelines [7,9]. In general, patients with complex multiple-vessel or more extensive disease were referred to CABG including CAD patients with significant left main disease and high anatomical complexity. Patients with less extensive CAD such as angina refractory to medical treatment and multivessel disease with less anatomical complexity underwent PCI. Medical therapy alone was indicated to treat angina in ischemic heart disease patients who were not eligible for PCI or CABG or have less severe disease.

Patients undergoing PCI or CABG also received medical therapy as a standard adjunctive therapy of revascularization.

2.3. Endpoints and follow-up

Patients who were able to return to our tertiary hospital following catheterization were followed. Follow-up continued for about 4 months after the last enrolled patient (February 2022). Follow-up duration was calculated relative to the admission date, which is usually the date of catheterization (index date). Echocardiographic evaluation was performed at admission and at follow-up using a two-dimensional imaging system (ALT HD1 6000 ht, 2–4 MHz probe, Philips Medical Systems Inc., Bothell, WA, USA) to evaluate left ventricular ejection fraction (LVEF) and left atrial size (LA diameter). The left atrial size was indexed to the body surface area.

The following clinical outcomes were evaluated at follow-up.

1. Echo evaluation of LVEF and LA size.
2. Major adverse cardiac and cerebrovascular events (MACCE) including MI, stroke, acute HF, ACS/angina requiring revascularization (excluding elective staged PCI patients or CABG), in-stent restenosis, morbidity, and mortality. Stroke was documented by non-contrast computed tomography (CT) or magnetic resonance imaging (MRI). Acute HF was established as a rapid onset of new or worsening signs and symptoms of HF with severe dyspnea, evidence of pulmonary congestion, or reduced perfusion. In stent restenosis was documented as stenosis greater than 50 % of the vessel lumen diameter of stented artery.
3. Atrial and ventricular tachyarrhythmias were documented by characteristic electrocardiogram.

Baseline plasma glucose/HbA1c, lipid contents, CBC, and other functional parameters for enrolled patients were retrieved from patients' electronic records. Plasma marker levels were evaluated and correlated with various clinical, biochemical, echocardiographic, and angiographic parameters among groups.

Table 1
Characteristics of patients with measured plasma ET-1.

Variable	No DM (n = 265)	DM (n = 225)	P value
Age	53.1 ± 0.63	57.4 ± 0.68	<0.0001*
Male gender, n (%)	208 (78.5)	152 (67.6)	0.0063*
BMI	29.7 ± 0.32	31.0 ± 0.36	0.0260*
Smoking	172 (64.9)	116 (51.7)	0.0033*
HT	152 (57.3)	193 (85.8)	<0.0001*
CAD	176 (66.4)	171 (76.0)	0.0200*
MI	35 (13.2)	17 (7.6)	0.0429*
HF	18 (6.8)	20 (8.9)	0.3872
Stroke/TIA	5 (1.9)	8 (3.6)	0.2520
CKD	10 (2.3)	11 (4.9)	0.1955
Type 1 DM	0	12 (5.3)	–
Type 2 DM	0	213 (94.7)	
Duration of DM, yr	0	8.5 ± 0.49	<0.0001*
PCI	84 (31.7)	75 (33.3)	0.700
CABG	13 (4.9)	17 (7.6)	0.2227
MT	79 (29.8)	79 (35.3)	0.1986
LDL	2.9 ± 0.07	2.6 ± 0.07	0.0108*
HDL	1.02 ± 0.02	1.04 ± 0.02	0.8942
Triglyceride	2.3 ± 0.08	2.6 ± 0.10	0.0251*
T. Cholesterol	4.7 ± 0.08	4.4 ± 0.08	0.0118*
HbA1c%	5.82 ± 0.06	8.4 ± 0.14	<0.0001*
Creatinine	78.5 ± 1.1	82.9 ± 2.5	0.7514
LVEF (%)	54.1 ± 0.006	52.5 ± 0.008	0.0140*
LA size, cm	3.7 ± 0.02	3.82 ± 0.03	0.0252
Beta blockers	150 (56.6)	150 (66.7)	0.0227*
ACEi	76 (28.7)	76 (33.8)	0.2240
ARBs	48 (18.1)	53 (23.6)	0.1378
Statins	200 (75.5)	214 (95.1)	<0.0001*
Aspirin	209 (78.9)	214 (95.1)	<0.0001*
OHA	2 (0.7)	183 (81.7)	<0.0001*
Insulin	0 (0)	86 (38.4)	<0.0001*

Data are expressed as n (%) for categorical variables and mean ± sem for continuous variables. BMI: body mass index; Hx: history; HT: hypertension; CAD: coronary artery disease MI: myocardial infarction; HF: heart failure; TIA: transient ischemic attack; CKD: chronic kidney disease; DM: diabetes mellitus; PCI: percutaneous coronary intervention; CABG: coronary artery bypass surgery; MT: medical therapy; LDL: low density low protein; HDL: high density lipoprotein; T. Cholesterol: total cholesterol; HbA1c: glycated hemoglobin; LVEF: left ventricular ejection fraction; LA: left atrium; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; OHA: oral hypoglycemic agents. Unit for serum lipids is mmol/L. * indicates significant statistical differences between groups relative to control using *t*-test or Mann-Whitney tests for continuous variables and Chi-square test for categorical variables ($p < 0.05$).

2.4. Measurements of plasma ET-1 levels

Plasma ET-1 levels were measured for 490 patients. A blood sample was withdrawn from the femoral artery of included patients before catheterization. Blood samples were transferred immediately on ice and centrifuged at 2500 rpm to isolate plasma. Samples were stored at −80 °C in the deep freezer until analysis. Analysis of samples was performed at one time after study termination. An ET-1 Quantikine enzyme-linked immunoassay kit was used to measure plasma ET-1 concentrations (DET100 ELISA; R&D Systems, Inc., MA, USA), as we previously described [3]. Briefly, the standards/samples were added to the coated wells and incubated at room temperature for 1 h on the shaker. Following washing, the conjugate was added and incubated at room temperature for 3 h. Wells were washed and incubated with the substrate solution, and then a stop solution was added. Absorbance intensity was measured using an Epoch Biotek microplate reader at a wavelength of 450 nm (Biotech, Winooski, VT, USA).

2.5. Statistical analysis

Data are shown as mean +standard error for continuous variables and frequencies for categorical variables. Univariate analysis utilizing two sample *t*-test was used to compare means between normally distributed continuous data (DM and non-DM patients). One-way analysis of variance (ANOVA) followed by Tukey's post hoc analysis was used to compare means between normally distributed data (e.g., age, BMI etc.) for multiple groups (CAD status and Revascularization strategies). The Mann-Whitney test was used to compare medians of non-normally distributed variables for DM and non-DM patients. Kruskal-Wallis tests followed by Dunn's post hoc analyses were applied to compare medians for non-normally distributed variables (e.g., plasma ET-1, creatinine, LVEF etc.) for multiple groups. Univariate analysis for categorical data (e.g., gender, disease history, use of medication etc.) was performed using Chi-square test. Correlation between continuous data (e.g., plasma ET-1 with lipids, LVEF and LA size) was assessed using Spearman

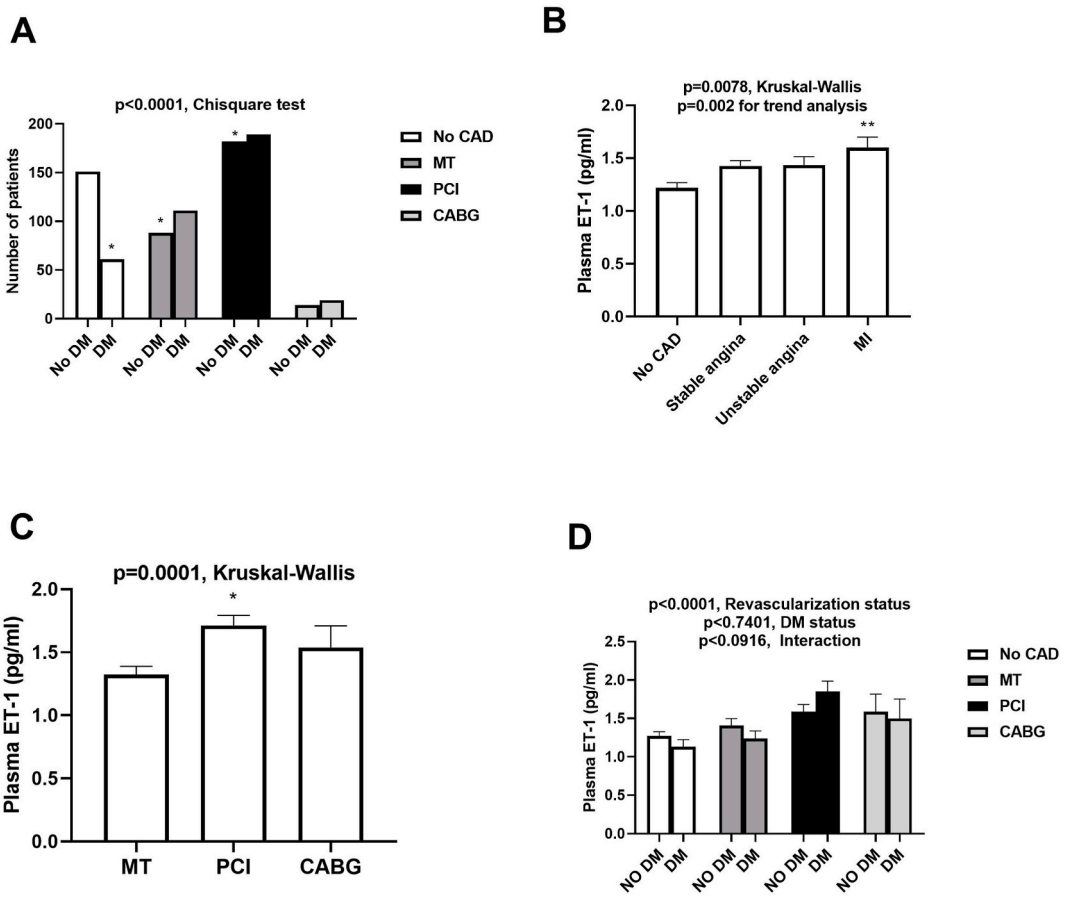


Fig. 1. Association of plasma ET-1 with revascularization and DM.
Fig. 1A represents number of patients with and without DM who received revascularization by percutaneous coronary intervention (PCI), coronary artery bypass surgery (CABG), or medical therapy (MT) in CAD and control patients without CAD, *p < 0.05. B represents plasma ET-1 levels among control patients without CAD, CAD patients with stable or unstable angina, and MI patients, *p < 0.05, **p < 0.01 vs. No CAD. C represents plasma ET-1 levels among patients who underwent PCI, CABG or received medical therapy, *p < 0.05 vs. MT. D represents plasma ET-1 levels among patients with and without DM per revascularization status.

correlation. Shapiro-Wilk test was used to check data normality. Because plasma ET-1 level was not normally distributed, a square root transformation was applied to perform multiple regression analysis that assumes data normality. The square root transformation effectively normalized the data. Standard least square multivariate analysis was conducted to adjust for other variables and possible confounders correlated with the square root of plasma ET-1 using a step-wise backward selection. Correlated variables were assessed using univariate analyses as described above. Univariate predictors with clinical significance and an entry p value ≤ 0.2 were assessed in the model and were removed if the exit p value was ≥ 0.3.

The Cox proportional hazard analysis was used to assess factors associated with the time (in days) until development of first cerebro/cardiovascular event. Sample size calculation was examined at a power of 90 % to detect differences in plasma ET-1 among study groups (Control, Medical therapy, PCI and CABG). Data were analyzed using JMP pro 13 software (SAS institute). Statistical significance was established at p-value <0.05. Figures were prepared using GraphPad Prism 9.

3. Results

3.1. Patients' characteristics

Table 1 shows study participants' characteristics stratified by DM status.

A total of 815 patients were enrolled, however, plasma ET-1 levels were measured in 490 patients (Supplementary Flow Diagram). About 46 % of them had DM, and 70.8 % had CAD (n = 347). Of these CAD patients, 49.3 % had DM (n = 171/347) and 15 % (n = 52/347) had MI. MI patients included 22 with ST segment elevated MI (STEMI) and 30 with non-STEMI. Among CAD patients, 159 underwent PCI, 30underwent CABG and 158 received medical therapy.

The prevalence of CAD was significantly higher in DM patients compared to non-DM patients (Odds ratio: 2.85, 95 % CI: 2.03–3.99, $p < 0.0001$). The proportion of DM patients who underwent CABG did not differ from those without DM (Fig. 1A). However, PCI was more frequently performed for DM patients compared to those without DM (41.7 % vs. 49.9 %, p = 0.0202, Table 1, Fig. 1A).

3.2. Association of plasma ET-1 levels with revascularization strategy, and the role of DM

Plasma ET-1 levels were measured in 490 random patients (Table 2).

Plasma ET-1 level was associated with CAD (p = 0.0029) and was higher in MI patients compared to controls (p = 0.0078, Fig. 1 B). A step wise increase in plasma ET-1 was observed with increasing severity of CAD status, as indicated by trend analysis (Fig. 1 B). Plasma ET-1 levels were not associated with DM (p = 0.288).

Plasma ET-1 levels were associated with revascularization; patients who underwent PCI demonstrated higher levels than those who received medical therapy, with a similar trend observed for CABG patients (Fig. 1C). The presence of DM did not have a significant impact on plasma ET-1 among PCI or CABG patients (Fig. 1D).

3.3. Univariate and multivariate predictors of plasma ET-1

Univariate predictors of plasma ET-1 were assessed according to DM status, Table 3. The square root transformation was applied to

Table 2
Univariate predictors of the square root plasma ET-1.

N = 490	No DM (N = 265)		DM (N = 225)	
Variable	P value	Beta	P value	Beta
Age	0.0526	1.95	0.6289	0.48
Male gender	0.0011*	3.289	0.7719	−0.290
BMI	0.5883	−0.54	0.7331	0.34
Smoking	0.0006*	3.49	0.6683	0.43
HT	0.7871	0.27	0.3612	0.92
CAD	0.0334*	2.138	0.0044*	2.877
PCI/CABG	0.0065*	2.75	<0.0001*	5.16
MT	0.5082	−0.662	0.0129*	−2.507
CKD	0.0806	1.75	0.5240	0.64
HF	0.6003	0.525	0.4067	0.831
Stroke/TIA	0.8459	−0.194	0.6716	−0.425
LA size, cm	0.4484	0.76	0.0518	1.97
LVEF%	0.0385*	−2.08	0.0016*	−3.22
LDL	0.0940	1.68	0.0032*	2.98
HbA1c%	0.3023	−1.03	0.5777	0.56
Creatinine	0.0916	1.69	0.0405*	2.06

BMI: body mass index; Hx: history; HT: hypertension; CAD: coronary artery disease MI: myocardial infarction; HF: heart failure; TIA: transient ischemic attack; CKD: chronic kidney disease; DM: diabetes mellitus; MT: medical therapy; PCI: percutaneous coronary intervention; CABG: coronary artery bypass surgery; LDL: low density low protein; HbA1c: glycated hemoglobin; LVEF: left ventricular ejection fraction; LA: left atrium; * Indicates presence of significant differences ($p < 0.05$).

Table 3
Independent predictors of plasma ET-1.

Response: square root ET-1 N = 490	No DM (N = 265)		DM (N = 225)	
Variable	Beta	P value	Beta	P value
PCI/CABG	1.7	0.0917	3.93	0.0001*
Medical therapy	–1.08	0.2803	−2.09	0.0386*
Age	0.93	0.3559	−0.61	0.5422
Male gender	1.66	0992	1.56	1221
Serum creatinine	0.35	0.7268	2.11	0.0364*
LVEF	−1.06	0.2895	−3.10	0.0024*

Beta (B) = slope/standard error. Revascularization status was coded as categorical variable: Control = 0, Medical therapy = 1, PCI/CABG = 2.

effectively normalize ET-1 levels.

Stratification by DM status revealed that a history of CAD, low LVEF, and elevated LDL and creatinine levels were correlated with increased plasma ET-1 among DM patients ($p < 0.05$). Plasma ET-1 was associated with the need for revascularization by PCI and CABG in both DM and non-DM patients, however, the effect size was notably higher for DM patients (p = 0065, Beta = 2.75 for non-DM vs. $p < 0.0001$, Beta = 5.16 for DM patients, Table 3). Interestingly, use of medical therapy was negatively correlated with plasma ET-1 in DM patients.

A multivariate analysis was performed to evaluate independent predictors of the square root of plasma ET-1 levels, adjusting for various variables and whether they are modified by DM status, Table 3.

Stratification by DM status showed that the correlation of plasma ET-1 with revascularization status was only significant among DM patients (Table 3). Interestingly, the use of medical therapy alone was associated with lower levels of plasma ET-1. In addition, low LVEF and elevated creatinine levels were associated with high levels of ET-1 (Table 3).

3.4. Association of plasma ET-1 with cerebro/cardiovascular events at short-term follow-up

Table 4 represents patients' characteristics at follow-up. A total of 366 patients returned for close follow-up. The median follow-up duration was 4 months (75th-25th interquartile range [IQR]: 7.13–1.42 months) with a mean of 5.28 ± 0.25 months. During this period, 132 patients experienced at least one cerebro/cardiovascular event, Table 4. The median time to the first event was 120 days (75th-25th IQR: 176-35 day). Most events occurred among DM patients (84 vs.48, Odds ratio: 2.04, 95 % CI: 1.3–3.2, p = 0.0013, Table 4). Among these events, 93 patients underwent catheterization due to new onset chest pain,14 had in-stent restenosis, and 10 patients died during follow-up, with four deaths attributed to non-cardiac conditions, Table 4.

Table 4
Patients' characteristics at follow-up.

Variable N = 366	First event (Yes) (n = 132)	First event (NO) (n = 234)	P value
Age	56.3 ± 0.88	55.5 ± 0.75	0.6801
Male gender, n (%)	77 (79.4)	115 (75.6)	0.4952
DM	84 (63.6)	108 (46.2)	0.0013*
Baseline HbA1c%	7.87 ± 0.20	7.26 ± 0.15	0.0032*
Square root ET-1	1.17 ± 0.03	1.21 ± 0.028	0.5431
Hx of MI	22 (16.7)	38 (16.2)	0.9155
Hx of HF	13 (9.8)	19 (8.1)	0.5438
FU LA size, cm	3.89 ± 0.02	3.81 ± 0.018	0.0275*
FU LVEF	49.6 ± 0.96	52.2 ± 0.55	0.1482
Prior PCI	78 (59.1)	124 (52.9)	0.2598
Prior CABG	5 (3.8)	14 (5.9)	0.3634
Prior MT	43 (32.8)	57 (24.4)	0.0820
FU MI	5 (3.78)	0 (0)	<0.0001*
FU Stroke/TIA	7 (5.30)	0 (0)	<0.0001*
FU VT	3 (2.27)	0 (0)	<0.0001*
FU AF	6 (4.54)	0 (0)	<0.0001*
FU AHF	5 (3.78)	0 (0)	<0.0001*
FU restenosis	14 (10.60)	0 (0)	<0.0001*
FU revascularization	82 (62.12)	0 (0)	<0.0001*
Death	10 (7.57)	0 (0)	<0.0001*

Data are expressed as n (%) for categorical variables and mean ± sem for continuous variables.; MI: myocardial infarction; FU: follow-up; TIA: transient ischemic attack; DM: diabetes mellitus; HF: heart failure, PCI: percutaneous coronary intervention; CABG: coronary artery bypass surgery; MT: medical therapy; LDL: low density low protein; LVEF: left ventricular ejection fraction; LA: left atrium; VT: ventricular tachycardia; AF: atrial fibrillation; AHF: acute heart failure. * Indicates significant statistical differences between groups relative to control using *t*-test or Mann-Whitney tests for continuous variables and Chi-square test for categorical variables ($p < 0.05$).

The square root of plasma ET-1 was not correlated with the probability of developing the first event at follow-up, Table 4. Similarly, prior revascularization by PCI or CABG was not associated with the probability of developing cerebrovascular or cardiovascular events ($p > 0.05$). However, baseline HbA1c% was higher in patients who developed the first event, Table 5. Multivariate analysis indicated that the probability of developing an event was not associated with the square root of plasma ET-1 ($p = 0.2055$).

Cox proportional hazard analysis revealed that DM was not associated with the time until the first event (adjusted HR = 0.85, $p = 0.4601$, 95 % CI 0.5514–1.320). Plasma ET-1 levels were not associated with the time until the first event in DM patients ($p = 0.1370$), Table 5. Prior revascularization by CABG was also not associated with an increased risk of first event in DM patients, (Table 5). No significant associations were found when adjusting for age and sex. However, prior revascularization by PCI was associated with a lower risk of the first event among DM patients (HR = 0.56, $p = 0.0316$, 95 % CI 0.333–0.949, Table 5). Conversely, there was a trend toward increased risk among DM patients treated with medical therapy.

4. Discussion

The aim of the present study was to assess the impact of plasma ET-1 levels on coronary revascularization choice upon admission, short-term clinical outcomes, and whether presence of DM modifies this impact. DM was more prevalent among CAD patients compared to those without CAD and was associated with the need for PCI. While plasma ET-1 was associated with CAD status, no association with DM was observed. However, plasma ET-1 levels were associated with the need for revascularization in DM patients. Despite the higher prevalence of cardiac and cerebrovascular events in DM patients, plasma ET-1 levels did not predict an increased risk of the first cerebro/cardiovascular event. Intriguingly, DM patients who underwent PCI at the first admission exhibited a lower risk of developing the first event.

4.1. Association of plasma ET-1 with the need for revascularization and the role of DM

Patients with DM have an increased risk of CVDs, notably for CAD, which is 2-4x higher compared to non-DM patients [10]. This augmented risk is attributed to factors like hyperglycemia, dyslipidemia, hypertension, and obesity [10].

DM patients typically exhibit complex multivessel disease that requires revascularization by PCI or CABG. The decision regarding the optimal revascularization procedure is challenging, and many patients may develop complications such as in-stent restenosis, leading to repeated revascularization [9]. The biological mechanisms underlying poor prognosis, restenosis, and repeated revascularization in DM patients are not completely understood. Hyperglycemia and insulin resistance exacerbate endothelial dysfunction in DM, partly through increased ET-1 levels. ET-1 is recognized as a potent vasoconstrictor, inflammatory factor, and mitogen, implicated in the pathophysiology of various cardiovascular diseases [3,11].

Plasma ET-1 levels were found to have increased in DM patients [12]. In our study, plasma ET-1 levels were associated with CAD rather than DM. We observed a stepwise increase in ET-1 levels from stable angina to myocardial infarction (MI), indicating its involvement in CAD severity and progression. Although plasma ET-1 has a short half-life [13], we could not determine whether elevated plasma ET-1 levels were chronic and contributed to ischemia development, or if they increased acutely following ischemia. Previously, it was found that plasma Big ET-1 (the precursor of ET-1) has a predictive value in CAD patients with three-vessel disease, MI, stable CAD, and DM [14–16]. We have also shown that plasma ET-1 is associated with the degree of coronary stenosis and the neutrophil/lymphocyte ratio, further supporting its role in the pathophysiology of CAD [3]. Notably, ET-1 levels were elevated in CAD patients, with the highest levels observed in those presenting within a week of MI, suggesting persistent ET-1 elevation following acute ischemia [3]. In DM, endothelial dysfunction often precedes vascular complications, thus, overexpression of vascular ET-1 may promote endothelial dysfunction leading to CAD [12].Interestingly, in streptozotocin (STZ) induced DM, DM promotes endothelial dysfunction, and this effect is more pronounced in ET-1 overexpressing mice [15], suggesting that DM may enhance the impact of ET-1 on endothelial dysfunction.

Although little is known about the utility of plasma ET-1 as a predictor for the need of revascularization in DM patients, our study reveals an association between plasma ET-1 levels and the need for PCI/CABG. Lower levels were observed in patients receiving medical therapy, indicating its association with CAD severity and progression. Notably, the relation of ET-1 to revascularization was only significant and independent among DM patients, indicating that DM may enhance the effect of ET-1 on CAD severity and act as an effect modifier, increasing the likelihood for revascularization by PCI or CABG. These findings offer new insights into the role of ET-1 in

Table 5
Factors associated with an increased risk of the first cerebro/cardiovascular event in DM patients.

Time (days) until first event in DM N = 192	Adjusted HR	95 % CI	P value
Plasma ET-1	0.744	0.4955–1.055	0.1017
HbA1c%	1.056	0.2882–1.144	0.9330
PCI	0.560	03336–0.949	0.0316*
CABG	1.440	0.4258–3.680	0.4955
MT	1.688	0.9806–2.850	0.0586
BMI	0.964	0.9110–1.014	0.1899

Analysis is adjusted to age and gender. HR: hazard ratio,.
DM: diabetes, PCI: percutaneous coronary intervention, CABG: coronary artery bypass surgery, MT: medical therapy, BMI: body mass index.

CAD progression in DM patients and its potential use in selecting patients for revascularization versus those who might benefit from medical therapy alone. The mechanisms underlying the predictive value of ET-1 in patients with DM are multifaceted. Increased ET-1 expression in CAD may worsen DM-induced endothelial dysfunction, promote oxidative damage, and lead to coronary remodeling, thereby increasing the need for revascularization [17]. In addition, vascular ET-1 or other inflammatory factors may cause platelet activation, which stimulates endothelial cells to release ET-1 leading to MI [18]. Moreover, ET-1 may inhibit nitric oxide production and promote calcium signaling uncoupling resulting in small blood vessels contraction, microcirculation disorder, and angina [19].

In ST segment elevated MI, elevated plasma ET-1 is associated with reperfusion injury and poor clinical outcome after PCI [20]. Our previous work showed that plasma ET-1 correlates with MI and the need for CABG, supporting its role in CAD development [3]. Low left ventricular function is a predictor of mortality and the correlation of plasma ET-1 with low LVEF suggests a potential impact on coronary artery blood flow [3]. We have also documented that increased left atrial ET-1 expression is strongly associated with enlarged left atrium [11]. Here we also observed a positive correlation of plasma ET-1 with enlarged left atria. Moreover, increased plasma ET-1 level was positively correlated with, creatinine level which also contributes to endothelial dysfunction and is recognized as a significant risk factor of CAD [21].

4.2. Impact of plasma ET-1 on poor clinical outcomes during follow-up and the role of DM

While our study has a limited follow-up period; approximately 36 % developed at least one cardiac/cerebrovascular event within a median of 4 months. Our institution, being a tertiary hospital, typically sees only critical cases for close follow-up shortly after catheterization, with stable patients often complete their follow-up at primary health centers. This could account for the limited duration of follow-up and the high number of events among the referred patients. Moreover, the frequency of revascularization and restenosis at follow-up may be influenced by the decision to perform PCI at the first admission for some patients who might be otherwise eligible for CABG, possibly due to patient anxiety and concerns about the surgery and its complications [22].

Despite the higher prevalence of cerebrovascular and cardiovascular events in DM patients-twice that of non-DM patients-there was no association between DM and the time to the first event. This suggests that while DM patients may be more likely to experience such events, they do not necessarily occur sooner compared to non-DM patients.DM patients are known to have an increased-risk of coronary in-stent restenosis [6]. Elevated plasma levels of big ET-1 were linked to an increased risk of adverse cardiovascular outcomes in patients with coronary in-stent restenosis and DM [6]. Studies also indicate that high plasma ET-1 levels correlate with increased risk of net adverse clinical events, all-cause and cardiovascular mortality, and primary cardiovascular events in patients with atrial fibrillation (AF) and acute coronary syndrome (ACS), as well as those undergoing PCI [19]. In addition, ET-1 has been identified as a strong predictor of major adverse cardiovascular events and 30-day mortality in patients with STEMI undergoing PCI [20] highlighting its potential role in disease progression.

However, in our study, plasma ET-1 was not associated with increased risk of the first event. This lack of association could be attributed to the relatively short follow-up period. Additionally, the inclusion of stable CAD and MI patients with diverse clinical prognoses might have influenced the results. Future investigations with larger number of patients comparing the clinical prognosis between MI and stable CAD are needed.

CABG has been found to be the preferred revascularization procedure for DM patients with multivessel disease [21], however, this finding was not replicated in meta-analyses [8]. In a small study [23], the five-year major adverse cardiac and cerebrovascular event (MACCE) rate in DM patients was higher in CABG patients compared to those undergoing stent PCI, though the MI and mortality rates were similar. In a well conducted long-term study, patients with DM and LV dysfunction who underwent CABG showed a lower incidence of MACE and longer survival rate compared to PCI patients [24].

In our study, PCI was more frequently performed than CABG in DM patients, and no association between CABG and the risk of the first event was found.

The limited number of patients undergoing CABG may affect its predictive value.

Remarkably, DM patients undergoing PCI independently exhibited a 44 % lower risk of the first cerebro/cardiovascular event compared to those undergoing CABG or receiving medical therapy. Conversely, an opposite trend was observed for patients treated solely with medical therapy. These findings indicate that PCI as a revascularization approach may improve clinical outcomes for DM patients with CAD, wheras medical therapy alone may worsen prognosis. Similar positive outcomes were noted for patients with LV dysfunction undergoing PCI compared to medical therapy alone [25]. Recent studies have also highlighted a risk reduction of MACE in DM patients undergoing PCI compared to those receiving medical therapy alone [14]. Given the limited number of CABG patients in our study, future studies with a larger, more homogeneous population and extended duration are recommended to better understand the optimal revascularization strategy for DM patients with CAD.

4.3. Limitations of the study

This is a prospective observational cohort study evaluating the predictive value of plasma ET-1 on the choice of revascularization and short-term follow-up based on DM status. While our findings establish a connection between ET-1 and the need for revascularization in DM patients, they do not prove a causal role of ET-1 on the severity of CAD. Limited funding constrained our ability to measure plasma ET-1 in only 490 randomly selected patients. Our study evaluated plasma ET-1 levels at baseline, lacking serial measurements during the follow-up that could offer a more comprehensive understanding of ET-1's prognostic value. Being a tertiary hospital, patients referred here often receive subsequent medical follow-up at primary centers and hospitals, potentially resulting in missed cerebro/cardiovascular events for those who did not return. Thus, the limited number of followed patients and the relatively

short duration of follow-up might have underestimated the prognostic value of plasma ET-1. Given the numerous analyzed variables and multiple comparison groups, the risk of chance findings may be substantial.

5. Conclusion

Our study documented that ET-1 was independently associated with the need for revascularization by PCI/CABG, predominantly among DM patients. While plasma ET-1 levels were not associated with the time until the first cerebro/cardiovascular events during follow-up, the prevalence of such events was notably higher among DM compared to non-DM patients. Notably, revascularization by PCI demonstrated a lower risk of the first event among DM patients. These insights may contribute to understanding the potential utility of plasma ET-1 in predicting the need for revascularization in DM patients and in selecting a revascularization strategy associated with minimal risk of cerebro/cardiovascular events.

Ethical statement

The study was reviewed and approved by the Institutional Review Board of King Abdullah University Hospital at Jordan University of Science and Technology (IRB # 20/130/2020, Date January 30, 2020), and was conducted according to the principles of the Declaration of Helsinki as revised in 2013. All participants provided a written informed consent.

Funding

This study was supported by the Deanship of Scientific Research; Jordan University of Science and Technology, Jordan (Grant number#: 119/2020).

Data availability

No data associated with the study has been deposited into a public repository. Raw data will be made available on request.

CRediT authorship contribution statement

Fadia Mayyas: Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Khalid Ibrahim:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Rasheed Ibdah:** Writing – review & editing, Supervision, Investigation. **Abdullah Al-Kasasbeh:** Writing – review & editing, Supervision, Investigation. **Muhannad J. Ababneh:** Writing – review & editing, Supervision, Investigation. **Ala'Eldin A. Ababneh:** Writing – review & editing, Supervision, Investigation. **Mohammad I. Jarrah:** Writing – review & editing, Supervision, Investigation. **Sukaina Rawashdeh:** Writing – review & editing, Visualization, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37777.

References

[1] J.A. Beckman, M.A. Creager, P. Libby, Diabetes and atherosclerosis: epidemiology, pathophysiology, and management, JAMA 287 (19) (2002) 2570–2581.
[2] F. Paneni, ESC/EASD guidelines on the management of diabetes and cardiovascular disease: established knowledge and evidence gaps, Diabetes Vasc. Dis. Res. 11 (1) (2013) 5–10, 2014.
[3] F. Mayyas, M. Al-Jarrah, K. Ibrahim, D. Mfady, D.R. Van Wagoner, The significance of circulating endothelin-1 as a predictor of coronary artery disease status and clinical outcomes following coronary artery catheterization, Cardiovasc. Pathol. : the official journal of the Society for Cardiovascular Pathology 24 (1) (2015) 19–25.
[4] J.G. Schneider, N. Tilly, T. Hierl, U. Sommer, A. Hamann, K. Dugi, et al., Elevated plasma endothelin-1 levels in diabetes mellitus, Am. J. Hypertens. 15 (11) (2002) 967–972.

[5] R. Lin, J. Junttila, J. Piuhola, E.S. Lepojarvi, J. Magga, A.M. Kiviniemi, et al., Endothelin-1 is associated with mortality that can be attenuated with high intensity statin therapy in patients with stable coronary artery disease, Commun. Med. 3 (1) (2023) 87.
[6] Y. Ma, T. Tian, T. Wang, J. Wang, H. Guan, J. Yuan, et al., Predictive value of plasma big endothelin-1 in adverse events of patients with coronary artery restenosis and diabetes mellitus: beyond traditional and angiographic risk factors, Front Cardiovasc Med 9 (2022) 854107.
[7] G.N. Levine, E.R. Bates, J.A. Bittl, R.G. Brindis, S.D. Fihn, L.A. Fleisher, et al., ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery, Circulation 134 (10) (2016) e123–e155, 2016.
[8] R. Seabra-Gomes, Percutaneous coronary interventions with drug eluting stents for diabetic patients, Heart 92 (3) (2006) 410–419.
[9] E.A. Amsterdam, N.K. Wenger, R.G. Brindis, D.E. Casey Jr., T.G. Ganiats, D.R. Holmes Jr., et al., 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Circulation 130 (25) (2014) e344–e426.
[10] A. Rawshani, A. Rawshani, S. Franzen, B. Eliasson, A.M. Svensson, M. Miftaraj, et al., Mortality and cardiovascular disease in type 1 and type 2 diabetes, N. Engl. J. Med. 376 (15) (2017) 1407–1418.
[11] F. Mayyas, M. Niebauer, A. Zurick, J. Barnard, A.M. Gillinov, M.K. Chung, et al., Association of left atrial endothelin-1 with atrial rhythm, size, and fibrosis in patients with structural heart disease, Circ Arrhythm Electrophysiol 3 (4) (2010) 369–379.
[12] C. González-Juanatey, M. Anguita-Sá Nchez, V. Barrios, I. Núñez-Gil, J.J. Gómez-Doblas, X. García-Moll, et al., Assessment of medical management in Coronary Type 2 Diabetic patients with previous percutaneous coronary intervention in Spain: a retrospective analysis of electronic health records using Natural Language Processing, PLoS One 17 (2) (2022) e0263277.
[13] K. Kostov, A. Blazhev, Circulating levels of endothelin-1 and big endothelin-1 in patients with essential hypertension, Pathophysiology 28 (4) (2021) 489–495.
[14] L. Guo, J. Wang, H. Ding, S. Meng, X. Zhang, H. Lv, et al., Long-term outcomes of medical therapy versus successful recanalisation for coronary chronic total occlusions in patients with and without type 2 diabetes mellitus, Cardiovasc. Diabetol. 19 (1) (2020) 100.
[15] C. Zhang, J. Tian, L. Jiang, L. Xu, J. Liu, X. Zhao, et al., Prognostic value of plasma big endothelin-1 level among patients with three-vessel disease: a cohort study, J Atheroscler Thromb 26 (11) (2019) 959–969.
[16] B.Y. Zhou, Y.L. Guo, N.Q. Wu, C.G. Zhu, Y. Gao, P. Qing, et al., Plasma big endothelin-1 levels at admission and future cardiovascular outcomes: a cohort study in patients with stable coronary artery disease, Int. J. Cardiol. 230 (2017) 76–79.
[17] N. Idris-Khodja, S. Ouerd, M.O.R. Mian, J. Gornitsky, T. Barhoumi, P. Paradis, et al., Endothelin-1 overexpression exaggerates diabetes-induced endothelial dysfunction by altering oxidative stress, Am. J. Hypertens. 29 (11) (2016) 1245–1251.
[18] I.A. Jagroop, S.S. Daskalopoulou, D.P. Mikhailidis, Endothelin-1 and human platelets, Curr. Vasc. Pharmacol. 3 (4) (2005) 393–399.
[19] M. Kalani, The importance of endothelin-1 for microvascular dysfunction in diabetes, Vasc. Health Risk Manag. 4 (5) (2008) 1061–1068.
[20] S.L.T. Pek, S.C. Lim, K. Ang, P.Y. Kwan, W.E. Tang, C.F. Sum, et al., Endothelin-1 predicts incident diabetic peripheral neuropathy in Type 2 Diabetes: a cohort study, Eur. J. Endocrinol. 182 (4) (2020) 429–438.
[21] S.D. Fihn, J.C. Blankenship, K.P. Alexander, J.A. Bittl, J.G. Byrne, B.J. Fletcher, et al., ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American college of cardiology/American heart association task force on practice guidelines, and the American association for thoracic surgery, preventive cardiovascular nurses association, society for cardiovascular angiography and interventions, and society of thoracic surgeons, J. Am. Coll. Cardiol. 64 (18) (2014) 1929–1949, 2014.
[22] Shahmansouri MK. Nazila, Seyed Hossein Ahmadi, Akram Arjmandi, Abbasali Karimi, Fear, anxiety, and beliefs about surgery in candidates patients for coronary artery bypass grafting, Eur. J. Exp. Biol. 2 (5) (2012).
[23] P.W. Serruys, A.T. Ong, L.A. van Herwerden, J.E. Sousa, A. Jatene, J.J. Bonnier, et al., Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial, J. Am. Coll. Cardiol. 46 (4) (2005) 575–581.
[24] J. Nagendran, S.J. Bozso, C.M. Norris, F.A. McAlister, J.J. Appoo, M.C. Moon, et al., Coronary artery bypass surgery improves outcomes in patients with diabetes and left ventricular dysfunction, J. Am. Coll. Cardiol. 71 (8) (2018) 819–827.
[25] G. Wolff, D. Dimitroulis, F. Andreotti, M. Kolodziejczak, C. Jung, P. Scicchitano, et al., Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: a meta-analysis, Circ Heart Fail 10 (1) (2017).