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RESEARCH LETTER

Relationship between body mass index and endogenous fibrinolytic status in 600 patients with ST-elevation myocardial infarction

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Impaired endogenous fibrinolysis is a strong, independent risk factor for recurrent cardiovascular events in patients with acute myocardial infarction (AMI),[1,2] but its determinants are not fully understood.

Obesity, defined as a body mass index (BMI) ≥30 kg/m^2, is an established risk factor for cardiovascular disease,[3] partly through its association with traditional risk factors, such as hypertension, diabetes, and dyslipidaemia,[4] with thrombotic risk mediated through altered metabolic pathways, chronic inflammation, and endothelial dysfunction.[5,6]

Plasminogen activator inhibitor-1 (PAI-1), a key natural inhibitor of fibrinolysis, is mainly secreted from the endothelium and activated platelets but can also be released by other tissues, such as adipose. Obesity has been associated with elevated PAI-1 activity, due to the increased size and frequency of adipocytes as well as enhanced gene expression in adipose cells.[6] A correlation between BMI and PAI-1 antigen and activity has been reported in individuals without established coronary disease.[7] However, the relationship between PAI-1 and BMI in individuals with cardiovascular disease is poorly understood.

In a single centre cohort study, we assessed the relationship between BMI and fibrinolytic status in 600 patients with ST-elevation myocardial infarction (STEMI). The cohort comprised of patients enrolled into 3 prospective studies (ClinicalTrials.gov identifier NCT02562690, EudraCT Number: 2018-003299-11 and UK Independent Research Application System ID no. 260786), approved by the UK Health Research Authority and local Research and Development board and conducted according to the principles outlined in the Declaration of Helsinki. The studies used near-identical sampling methods and inclusion/exclusion criteria, ensuring valid cohort assembly without introducing differences in BMI or risk-factor profiles. All patients gave informed consent. Patients on anticoagulation, with coagulopathy, thrombocytopenia, end-stage renal failure, sepsis, alcohol dependence, or in an investigational trial were excluded. Patient demographics, history, medications, routine blood results, weight, and height were recorded on admission, and BMI calculated [weight (kg)/height^2 (m)]. Individuals were grouped into BMI categories using the World Health Organization classification.[8]

A blood sample was taken from patients with STEMI upon admission, after dual antiplatelet therapy but before angiography or administration of anticoagulation. The first 5 mL blood was used for routine tests including coagulation and hs-CRP, and the next 5 mL non-anticoagulated blood tested using the automated point-of-care Global Thrombosis Test (Thromboquest Ltd., UK),[1] with measurement started within 15 s of blood draw. Briefly, flowing blood is subjected to high-shear, resulting in platelet activation and activation of coagulation. The time until occlusive thrombus formation (occlusion time) and subsequent restart of flow due to endogenous thrombolysis (lysis time) are recorded. A further 5 mL citrated blood was centrifuged (2300 × g for 10 min) to yield platelet-poor-plasma and PAI-1 antigen level measured with a commercial ELISA kit (ab269373; Abcam, Cambridge, UK) in randomly selected subgroup of 105 patients, chosen to achieve an even distribution of lysis times and roughly equal representation across the five BMI groups (except underweight).

Differences across BMI categories were assessed using the chi-square test for dichotomous variables, with one-way analysis of variance or Kruskal–Wallis test for continuous variables. Quade's nonparametric ANCOVA was used to compare groups while adjusting for covariates. Spearman's correlation coefficient was used. Analyses were performed using SPSS v29.0 (IBMCorp), with $P < 0.05$ taken to indicate significance.

In total, 600 patients were recruited (79% male), classified as normal weight ($n = 181$), overweight ($n = 208$), obese with BMI ≥30 kg/m^2 ($n = 203$), or underweight ($n = 8$). Individuals with higher BMI were younger, more often had diabetes and higher hs-CRP (*Figure 1*).

BMI was not associated with thrombotic occlusion or endogenous fibrinolysis time, fibrinogen or PAI-1 antigen levels, even after

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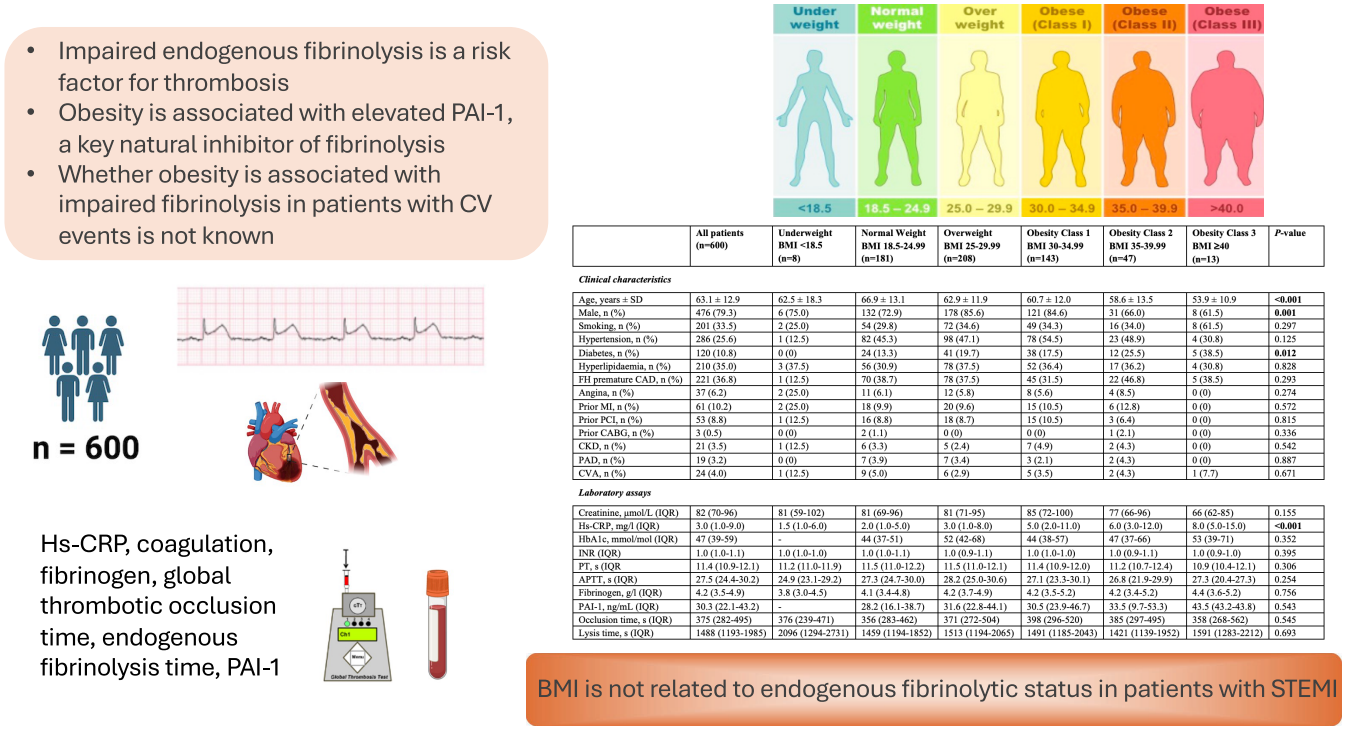

	All patients (n=600)	Underweight BMI <18.5 (n=8)	Normal Weight BMI 18.5-24.99 (n=181)	Overweight BMI 25-29.99 (n=208)	Obesity Class 1 BMI 30-34.99 (n=143)	Obesity Class 2 BMI 35-39.99 (n=47)	Obesity Class 3 BMI ≥40 (n=13)	*P*-value
Clinical characteristics								
Age, years ± SD	63.1 ± 12.9	62.5 ± 18.3	66.9 ± 13.1	62.9 ± 11.9	60.7 ± 12.0	58.6 ± 13.5	53.9 ± 10.9	**<0.001**
Male, n (%)	476 (79.3)	6 (75.0)	132 (72.9)	178 (85.6)	121 (84.6)	31 (66.0)	8 (61.5)	**0.001**
Smoking, n (%)	201 (33.5)	2 (25.0)	54 (29.8)	72 (34.6)	49 (34.3)	16 (34.0)	8 (61.5)	0.297
Hypertension, n (%)	286 (25.6)	1 (12.5)	82 (45.3)	98 (47.1)	78 (54.5)	23 (48.9)	4 (30.8)	0.125
Diabetes, n (%)	120 (10.8)	0 (0)	24 (13.3)	41 (19.7)	38 (17.5)	12 (25.5)	5 (38.5)	**0.012**
Hyperlipidaemia, n (%)	210 (35.0)	3 (37.5)	56 (30.9)	78 (37.5)	52 (36.4)	17 (36.2)	4 (30.8)	0.828
FH premature CAD, n (%)	221 (36.8)	1 (12.5)	70 (38.7)	78 (37.5)	45 (31.5)	22 (46.8)	5 (38.5)	0.293
Angina, n (%)	37 (6.2)	2 (25.0)	11 (6.1)	12 (5.8)	8 (5.6)	4 (8.5)	0 (0)	0.274
Prior MI, n (%)	61 (10.2)	2 (25.0)	18 (9.9)	20 (9.6)	15 (10.5)	6 (12.8)	0 (0)	0.572
Prior PCI, n (%)	53 (8.8)	1 (12.5)	16 (8.8)	18 (8.7)	15 (10.5)	3 (6.4)	0 (0)	0.815
Prior CABG, n (%)	3 (0.5)	0 (0)	2 (1.1)	0 (0)	0 (0)	1 (2.1)	0 (0)	0.336
CKD, n (%)	21 (3.5)	1 (12.5)	6 (3.3)	5 (2.4)	7 (4.9)	2 (4.3)	0 (0)	0.542
PAD, n (%)	19 (3.2)	0 (0)	7 (3.9)	7 (3.4)	3 (2.1)	2 (4.3)	0 (0)	0.887
CVA, n (%)	24 (4.0)	1 (12.5)	9 (5.0)	6 (2.9)	5 (3.5)	2 (4.3)	1 (7.7)	0.671
Laboratory assays								
Creatinine, µmol/L (IQR)	82 (70-96)	81 (59-102)	81 (69-96)	81 (71-95)	85 (72-100)	77 (66-96)	66 (62-85)	0.155
Hs-CRP, mg/l (IQR)	3.0 (1.0-9.0)	1.5 (1.0-6.0)	2.0 (1.0-5.0)	3.0 (1.0-8.0)	5.0 (2.0-11.0)	6.0 (3.0-12.0)	8.0 (5.0-15.0)	**<0.001**
HbA1c, mmol/mol (IQR)	47 (39-59)	-	44 (37-51)	52 (42-68)	44 (38-57)	47 (37-66)	53 (39-71)	0.352
INR (IQR)	1.0 (1.0-1.1)	1.0 (1.0-1.0)	1.0 (1.0-1.1)	1.0 (0.9-1.1)	1.0 (1.0-1.0)	1.0 (0.9-1.1)	1.0 (0.9-1.0)	0.395
PT, s (IQR	11.4 (10.9-12.1)	11.2 (11.0-11.9)	11.5 (11.0-12.2)	11.5 (11.0-12.1)	11.4 (10.9-12.0)	11.2 (10.7-12.4)	10.9 (10.4-12.1)	0.306
APTT, s (IQR)	27.5 (24.4-30.2)	24.9 (23.1-29.2)	27.3 (24.7-30.0)	28.2 (25.0-30.6)	27.1 (23.3-30.1)	26.8 (21.9-29.9)	27.3 (20.4-27.3)	0.254
Fibrinogen, g/l (IQR)	4.2 (3.5-4.9)	3.8 (3.0-4.5)	4.1 (3.4-4.8)	4.2 (3.7-4.9)	4.2 (3.5-5.2)	4.2 (3.4-5.2)	4.4 (3.6-5.2)	0.756
PAI-1, ng/mL (IQR)	30.3 (22.1-43.2)	-	28.2 (16.1-38.7)	31.6 (22.8-44.1)	30.5 (23.9-46.7)	33.5 (9.7-53.3)	43.5 (43.2-43.8)	0.543
Occlusion time, s (IQR)	375 (282-495)	376 (239-471)	356 (283-462)	371 (272-504)	398 (296-520)	385 (297-495)	358 (268-562)	0.545
Lysis time, s (IQR)	1488 (1193-1985)	2096 (1294-2731)	1459 (1194-1852)	1513 (1194-2065)	1491 (1185-2043)	1421 (1139-1952)	1591 (1283-2212)	0.693

Figure 1 Relationship between endogenous fibrinolysis and body mass index among patients with ST-segment elevation myocardial infarction. Values are presented as n (%) or median (interquartile range, IQR) as indicated. Values in bold are significant (i.e. $P < 0.05$). Abbreviations: AMI, acute myocardial infarction; APTT, activated partial thromboplastin time; BMI, body mass index; CABG, coronary artery by-pass grafting; CKD, chronic kidney disease; CV, cardiovascular; CVA, cerebrovascular accident; FH premature CAD, family history of premature cardiovascular disease; HbA1c, haemoglobin A1c; Hs-CRP, high sensitivity C-reactive protein; INR, international normalized ratio; LT, lysis time; OT, occlusion time; PAD, peripheral arterial disease; PAI-1, plasminogen activator inhibitor 1; PCI, percutaneous coronary intervention; PT, prothrombin time; STEMI, ST-segment elevation myocardial infarction.

adjustment for covariates, and no associations were observed across sex or diabetes strata or when stratified by BMI. BMI was weakly correlated with hs-CRP ($r = 0.266$, $P < 0.001$) and inversely with prothrombin time ($r = -0.102$, $P = 0.019$). Occlusion time was weakly correlated with hs-CRP ($r = 0.128$, $P = 0.003$) and inversely with platelet count ($r = -0.106$, $P = 0.01$).

Impaired fibrinolysis, found in ~1 in five patients with STEMI, is a marker of residual cardiovascular risk.[1] However, our results indicate that BMI is not associated with endogenous fibrinolysis in STEMI patients. Although easy to calculate, BMI is a poor measure of adiposity, since it cannot differentiate between fat mass and lean body mass, and fails to account for variations in body composition related to age, sex, or ethnicity. In healthy individuals, PAI-1 activity correlates modestly with BMI ($r = 0.4$, $P < 0.001$),[9] and animal studies show that obesity, particularly visceral fat, can increase PAI-1 production, promoting clot formation.[10] Elevated plasma PAI-1 levels have been associated with excessive visceral rather than subcutaneous fat, particularly central adiposity, suggesting that fat distribution may influence fibrinolytic balance.[6,10] Waist-to-hip ratio, a more accurate marker of visceral fat distribution, correlated more closely with PAI-1 levels than BMI in obese women.[11] The contribution of subcutaneous adipose tissue to PAI-1 expression or activity is contentious, although its location may be relevant, with PAI-1 expression in the subcutaneous abdominal depot, but not in femoral fat, influencing circulating PAI-1 levels.[12]

Earlier association of BMI with circulating PAI-1 levels were reported predominantly in healthy individuals and/or in non-acute settings, whereas in our study, measurements were taken during the AMI presentation. As PAI-1 is an acute-phase reactant, measurements during AMI may not reflect the stable/chronic state. Additionally, endothelial cells, hepatocytes and platelets can all contribute substantially to circulating PAI-1 levels.[13] We did not observe a relationship between PAI-1 level and endogenous fibrinolysis, which could signal that PAI-1 activity may be more important than protein levels during AMI, when PAI-1 may already be maximally activated, or other factors such as fibrin structure and/or plasmin inhibitor levels determine fibrinolytic status. Moreover, a significant proportion of PAI-1 is stored in platelets[13] and released upon platelet activation, so that circulating PAI-1 level may not reflect the total PAI-1 available to inhibit fibrinolysis, especially at sites of thrombosis.

Limitations include the small number of patients within each BMI band, which were not matched for age or diabetes status. BMI does not capture total adiposity or its distribution, which were not documented and may misclassify cardiometabolic risk. The single measurement of thrombotic status in STEMI may not reflect the stable/chronic state, and antiplatelet medications could have affected fibrinolytic status, although previously were not shown to do so.[1] Finally, the predominantly Caucasian male population may not be representative of other cohorts.

In conclusion, we found no association between endogenous fibrinolysis and body mass in patients with STEMI. Whether in the chronic state, endogenous fibrinolysis is related to BMI or visceral fat, requires further study.

Authors' contributions

J.H.L.—concept and design of the work, analysis of data, interpretation, initial draft of manuscript and revisions. G.V.—interpretation of results, critical review of the manuscript and approving final version. R.A.A.—interpretation of results, critical review of the manuscript and approving final version. R.K.—data acquisition, analysis and critical review. Y.X.G.—data acquisition, analysis and critical review. M.F.—data acquisition, analysis and critical review. D.A.G.—concept and design, critical analysis, interpretation, revisions and final approval.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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