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Endothelial Dysfunction in Non-Diabetic Patients and Coronary Calcification: A Different Pathway to Coronary Artery Disease?

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SOUHRN

Cíl: Cílem studie bylo posoudit, zda je endoteliální dysfunkce (ED) u pacientů s ischemickou chorobou srdeční (ICHS) spojena s nižší prevalencí koronárních makrokalcifikací (CMC), jež představují marker pokročilejší a obvykle stabilnější remodelace aterosklerotického plátu.
Metody: Tato sekundární analýza zahrnovala 77 konsekutivních pacientů zařazených do studie FiGARO. Endoteliální funkce byla hodnocena pomocí přístroje EndoPAT 2000, přičemž ED byla definována jako index reaktivní hyperemie (RHI) < 1,67. Koronární angiogramy byly retrospektivně přehodnoceny zaslepenými hodnotiteli s cílem stanovit přítomnost angiograficky patrných makrokalcifikací. Pacienti byli rozděleni do tří, předem definovaných skupin: diabetici, nediabetici se zachovanou endoteliální funkcí (RHI ≥ 1,67) a nediabetici s ED. Mezi skupinami byly porovnány klinické charakteristiky, tradiční rizikové faktory a angiografické nálezy. Nezávislé prediktory CMC byly identifikovány pomocí logistické regrese.
Výsledky: Endoteliální dysfunkce byla přítomna u 21 pacientů (27,3 %) a diabetes mellitus u 24 pacientů (31,2 %). Celková prevalence CMC činila 22,1 %. U nediabetických pacientů se prevalence CMC významně lišila mezi endoteliálními fenotypy: 31,6 % u osob se zachovanou endoteliální funkcí oproti 8,8 % u osob s ED (p = 0,04). Nediabetičtí pacienti s ED vykazovali nejnižší prevalenci CMC, a to navzdory obdobnému věku i zátěži rizikovými faktory. Zachovaná endoteliální funkce byla u nediabetiků nezávislým prediktorem přítomnosti CMC (poměr šancí [OR] 4,77; 95% poměr spolehlivosti [CI] 1,03–22,0; p = 0,045), přičemž tento vztah přetrval i po adjustaci na věk, dyslipidemii, arteriální hypertenzi, chronické onemocnění ledvin a aktivní kouření (OR 6,96; 95% CI 1,27–38,19; p = 0,026).
Závěry: U nediabetiků s ICHS je endoteliální dysfunkce spojena s výrazně nižší prevalencí koronárních makrokalcifikací, což naznačuje převahu nekalcifikovaného aterosklerotického fenotypu. Tato zjištění podporují koncept odlišných mechanismů aterogeneze, v jejichž rámci ED bez současných metabolických abnormalit odráží časnější, zánětlivě podmíněnou vaskulární patologii, nikoli pokročilou remodelaci spojenou s makrokalcifikacemi. Neinvazivní hodnocení endoteliální funkce tak může přispět k přesnějšímu odhadu rizika identifikací pacientů, kteří s vyšší pravděpodobností nesou nekalcifikované a potenciálně vulnerabilní pláty, a poskytovat tak doplňkovou informaci nad rámec tradičních kardiovaskulárních rizikových faktorů.

ABSTRACT

Objective: To evaluate whether endothelial dysfunction (ED) in patients with coronary artery disease (CAD) is associated with a lower prevalence of coronary macrocalcifications (CMC), a marker of more advanced and typically more stable plaque remodelling.
Methods: This secondary analysis included 77 consecutive patients enrolled in the FIGARO trial. Endothelial function was evaluated using the EndoPAT 2000 device, with ED defined as RHI <1.67. Coronary angiograms were re-assessed by blinded reviewers for the presence of angiographically visible macrocalcification. Patients were categorised into three predefined groups: diabetics, non-diabetics with preserved endothelial function (RHI ≥1.67), and non-diabetics with ED. Clinical characteristics, risk factors, and angiographic fin-

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dings were compared across groups. Logistic regression was used to identify independent predictors of CMC.
Results: ED was present in 21 patients (27.3%), and diabetes mellitus in 24 (31.2%). Overall, CMC was identified in 22.1% of the cohort. Among non-diabetic patients, the prevalence of CMC differed markedly across endothelial phenotypes: 31.6% in non-diabetics with preserved endothelial function versus only 8.8% in non-diabetics with ED ($p = 0.04$). Despite similar age and risk-factor burden, non-diabetic patients with ED had the lowest prevalence of CMC. In non-diabetics, preserved endothelial function independently predicted the presence of CMC (OR 4.77, 95% CI 1.03–22.0; $p = 0.045$). This association remained significant in multivariable analysis adjusting for age, dyslipidaemia, arterial hypertension, CKD, and active smoking (OR 6.96, 95% CI 1.27–38.19; $p = 0.026$).
Conclusions: Among non-diabetic patients with CAD, endothelial dysfunction is associated with a markedly lower prevalence of coronary macrocalcification, indicating a non-calcified atherosclerotic phenotype. These findings support the concept of divergent atherosclerotic pathways, in which ED without metabolic abnormalities reflects earlier, inflammation-driven vascular pathology rather than calcific remodelling. Non-invasive endothelial function testing may help refine risk stratification by identifying patients more likely to harbour non-calcified and potentially vulnerable plaques, thereby providing complementary information beyond traditional cardiovascular risk factors.

Keywords:
Coronary artery disease
Coronary calcification
Coronary pathophysiology
Endothelial dysfunction

Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide and arises through multiple pathogenetic pathways that share common risk factors but produce distinct morphological and clinical phenotypes of atherosclerosis. The classical model describes a chronic process driven by lipid infiltration, inflammation, oxidative stress, and endothelial dysfunction (ED), yet emerging evidence demonstrates that atherosclerosis is a heterogeneous disease whose dominant biological drivers vary considerably among individuals.[1]

Coronary calcification comprises a spectrum of mineralization patterns ranging from early microcalcifications to extensive macrocalcified deposits. Microcalcifications, detected as part of coronary artery calcium scoring during computed tomography, are thought to reflect active inflammatory processes and have been associated with plaque vulnerability and higher acute event risk.[2,3] In contrast, dense macrocalcifications, detectable on invasive coronarography – large, radiopaque calcific deposits corresponding to advanced fibrocalcific plaque – represent later, consolidated stages of atherosclerosis and are generally associated with greater plaque stability and lower propensity to rupture compared with non-calcified or microcalcified plaques.[4,5]

ED is widely recognized as an early and pivotal event in atherogenesis. It results from reduced nitric oxide bioavailability, increased oxidative stress, inflammatory activation, and impaired vascular homeostasis, and can be assessed through invasive or non-invasive techniques such as peripheral arterial tonometry (PAT).[6] Although ED is universally accepted as a risk factor for atherosclerosis,[7] its downstream consequences appear to differ depending on the aetiology of endothelial injury. In diabetes mellitus (DM) and metabolic syndrome, ED is driven predominantly by metabolic disturbances – including hyperglycaemia, insulin resistance, dyslipidaemia, and accumulation of advanced glycation end products – which promote endothelial activation, inflammation, and pro-calcific vascular remodelling.[8,9] Experimental and clinical studies have shown that in these condition, the ED accompanies accelerated osteogenic transformation of vascular smooth muscle cells, endothelial-to-mesenchymal transition, and ultimately vascular and coronary calcification.[10,11] In contrast, ED arising in the absence of metabolic dysregulation – such as that associated with hypertension, smoking, inflammatory stress, or impaired shear-stress signalling – may represent a biologically distinct phenotype and appears to reflect primarily inflammatory and functional endothelial impairment without the metabolic triggers known to drive calcific remodelling and as a consequence, it may be associated with earlier or predominantly non-calcified forms of atherosclerosis.[12] Non-invasive ED assessment using flow-mediated dilation or peripheral arterial tonometry has shown consistent associations with cardiovascular events; however, the evidence for its incremental predictive value beyond traditional risk factors remains limited to high risk population undergoing invasive coronarography.[13]

Based on this conceptual framework, we hypothesized that ED in non-diabetic patients with CAD could be associated with a distinct, predominantly non-macro calcified atherosclerotic phenotype with higher risk of plaque instability, whereas preserved endothelial function in non-diabetic patients is associated with macrocalcification burden similar to atherosclerosis phenotype in patients with diabetes.

Methods

We performed a secondary analysis of consecutive patients with known CAD enrolled in the FiGARO trial (NCT03033810), an international, multicentre prospective study comparing discrepancies between fractional-flow reserve (FFR) and instantaneous wave-free ratio (iFR) in the evaluation of coronary lesions.[14] The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee of the General University Hospital in Prague. All participants provided written informed consent prior to enrolment.

Endothelial function was evaluated by reactive-hyperaemia peripheral artery tonometry (RH-PAT) technique using the EndoPAT 2000 device (Itamar Medical, Caesarea, Israel), a validated peripheral arterial tonometry sys-

tem.[15] All examinations were performed according to the standard protocol in a quiet, temperature-controlled environment after an overnight fast and withholding vasoactive medications. Patients rested supine for at least 15 minutes before testing. Fingertip probes recorded pulse amplitude at baseline and during reactive hyperaemia induced by 5-minute brachial artery occlusion.[16] The device automatically calculated the reactive hyperaemia index (RHI); RHI values <1.67 were considered indicative of ED in accordance with published studies.[15,17]

Coronary angiograms of all included patients were re-evaluated for the presence of coronary macrocalcification (CMC) by two independent reviewers blinded to the ED results. Angiographically visible calcification was defined according to established interventional criteria as radiopaque, intraluminal or vessel-wall calcific deposits identifiable on fluoroscopy.[18] Calcification visible before contrast injection and in more than one projection were classified as CMC.

Baseline characteristics, including cardiovascular risk factors – body mass index (BMI), diabetes mellitus, arterial hypertension, dyslipidaemia, smoking status, chronic kidney disease (CKD), were obtained from clinical records and physical examinations.

Table 1 – Baseline characteristics of study population

Variable	N (%); median (IQR) / mean (SD)
Age	67.00 (13.00)
Female	16 (20.78%)
Height (cm)	175.00 (10.00)
Weight (kg)	90.00 (20.00)
BMI (kg/m^2)	28.95 (6.29)
Diabetes mellitus	24 (31.17%)
Arterial hypertension	59 (76.62%)
Dyslipidaemia	52 (67.53%)
CKD	9 (11.69%)
COPD	13 (16.88%)
Smoking history	58 (75.32%)
Current smoker	32 (41.56%)
PAD	17 (22.08%)
Coronary macrocalcification	17 (22.08%)
RHI	1.47 (0.42)
LVEF (%)	60.00 (18.00)
Hb (g/l)	138.50 (22.25)
WBC	8.23 (3.55)
Creatinine	84.00 (26.50)
LM stenosis	13 (17.57%)
LAD stenosis	31 (40.26%)

BMI – body mass index; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; IQR – interquartile range; Hb – hemoglobin; LAD – left anterior descending artery; LM – left main artery; LVEF – left ventricle ejection fraction; N – number of participants; PAD – peripheral artery disease; RHI – reactive hyperemia index; SD – standard deviation; WBC – white blood cell count.

For purposes of analysis, first the patients with/without ED were compared, second the population was divided into three subgroups – diabetics, non-diabetics without ED; non-diabetics with ED. Continuous variables are reported as mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for skewed data. Categorical variables are presented as counts and percentages. Group differences were assessed using the Student's t-test for continuous variables and the χ^2 test for categorical variables. Logistic regression was used for uni- and multivariate testing. All tests were two-sided, and *p*-values <0.05 were considered statistically significant. Statistical analyses were performed using R version 4.4.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 77 patients were included (median age 67 years; 20.8% females). Baseline characteristics are summarized in **Table 1**.

Diabetes mellitus was present in 24 patients (31.2%), while endothelial dysfunction (RHI < 1.67) was observed in 21 patients (27.3%).

Compared with patients without ED, those with ED had significantly higher prevalence of diabetes (9.5% vs. 39.3%, $p = 0.03$) as depicted in **Table 2.**

No significant differences were found in age, smoking status, dyslipidaemia, presence of CKD, or prevalence of prior acute myocardial infarction. However, the trend towards higher prevalence of peripheral artery disease in patients with endothelial dysfunction was observed

Table 2 – Differences between patients with and without endothelial dysfunction

Comorbidity	RHI >1.67	RHI <1.67	*p*-value
Total	21 (27.3%)	56 (72.7%)	
Male	15 (71.4%)	46 (82.1%)	0.47
Discrepancy	11 (52.4%)	20 (35.7%)	0.29
AMI history	9 (42.9%)	24 (42.9%)	1.00
Diabetes mellitus	2 (9.5%)	22 (39.3%)	**0.03**
Arterial hypertension	14 (66.7%)	45 (80.4%)	0.34
Dyslipidaemia	11 (52.4%)	41 (73.2%)	0.14
CKD	2 (9.5%)	7 (12.5%)	1.00
Stroke history	2 (9.5%)	4 (7.1%)	1.00
COPD	4 (19.0%)	9 (16.1%)	1.00
Smoking history	15 (71.4%)	43 (76.8%)	0.85
Current smoker	8 (38.1%)	24 (42.9%)	0.91
PAD	1 (4.8%)	16 (28.6%)	0.05
Coronary macrocalcification	7 (33.3%)	10 (17.9%)	0.25

AMI – acute myocardial infarction; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; PAD – peripheral artery disease; RHI – reactive hyperemia index.

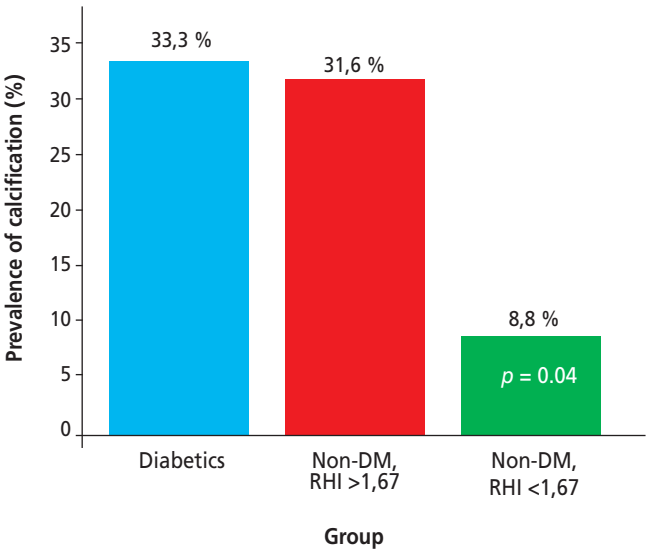

Fig. 1 – Differences in prevalence of coronary calcification according to diabetes or ED status.

Coronary macrocalcification was present in 22.1% of the entire cohort. When patients were stratified into three predefined phenotypic groups — diabetics, non-diabetics without ED, and non-diabetics with ED — a significant difference in CMC prevalence emerged as shown in **Figure 1**.

Non-diabetic patients with ED also exhibited the lowest prevalence of CMC despite comparable age and risk-factor burden (**Table 3**).

Among non-diabetic patients, presence of normal endothelial function (RHI >1.67) independently predicted the presence of CAC (OR 4.77, 95% CI 1.03–22.0; p = 0.045).

In a multivariable logistic regression model restricted to non-diabetic patients and including age, dyslipidaemia, arterial hypertension, CKD, and active smoking as covariates, RHI >1.67 remained a strong and independent predictor of CMC (OR 6.96, 95% CI 1.27–38.19; p = 0.026). None of the traditional risk factors reached statistical significance in this model (**Supplementary material 1**).

Discussion

In this study, we demonstrate that among non-diabetic patients with established CAD, the presence of endothelial dysfunction (ED) as assessed by the RHI-PAT method is associated with a markedly lower prevalence of coronary macrocalcification. This observation suggests that, in the absence of diabetes, ED may signal a distinct atherosclerotic phenotype characterized predominantly by non-calcified plaque components.

Previous work has shown that diverse pathogenic pathways shape the morphology of atherosclerotic plaques. Metabolic dysregulation – as seen in diabetes mellitus or chronic kidney disease – has consistently been linked to an increased burden of coronary artery calcium and more advanced mineralized atherosclerosis.[19,20] Our findings extend these observations by demonstrating that non-diabetic CAD patients with ED exhibit significantly fewer coronary macrocalcifications compared with both non-diabetic individuals without ED and with diabetic patients. Although ED is commonly observed in diabetes,[21] its presence in non-diabetic individuals likely reflects alternative mechanisms—such as inflammation, impaired nitric oxide bioavailability, endothelial activation, or prothrombotic imbalance—that promote the formation of non-calcified or minimally calcified plaques rather than mineralized lesions.

The inverse association between ED and coronary macrocalcification in non-diabetic patients may therefore reflect different stages of plaque evolution. Macrocalcification represents a late and largely reparative phase of atherosclerosis,[4] whereas ED in the absence of metabolic disease corresponds to an earlier, inflammation-driven phenotype characterized by diminished nitric oxide signalling, endothelial activation, and increased vascular permeability.[12] These processes favour the formation of non-calcified plaques but do not provide the osteogenic stimulus required for advanced mineralization.[11] By excluding patients with diabetes – where ED develops within a pro-calcific metabolic milieu – our data isolate a non-metabolic ED phenotype linked to less mature, less mineralized plaque architecture, providing a coherent mechanistic basis for the markedly lower prevalence of macrocalcification observed in this subgroup.

Table 3 – Differences between patients divided by presence of diabetes mellitus and endothelial dysfunction

Parameter	Diabetics	Non-diabetics preserved RHI	Non-diabetics, reduced RHI	*p*-value
Age (median, IQR)	69.0 (IQR 9.75)	65.0 (IQR 14.50)	65.5 (IQR 11.25)	0.47
Smoking history (%)	75.0%	68.4%	79.4%	0.67
Current smoker (%)	20.8%	42.1%	55.9%	0.03
Arterial hypertension (%)	91.7%	63.2%	73.5%	0.08
Dyslipidaemia (%)	87.5%	47.4%	64.7%	0.02
CKD (%)	16.7%	10.5%	8.8%	0.65
Triple-vessel disease (%)	70.8%	52.6%	55.9%	0.40
Coronary calcification (%)	33.3%	31.6%	8.8%	0.04

CKD – chornic kidney disease; RHI – reactive hyperaemia index.

Importantly, accumulating evidence indicates that the degree of coronary calcification is not only a marker of plaque burden but also of plaque stability. Dense macrocalcifications are repeatedly associated with a lower risk of major adverse cardiovascular events (MACE), whereas non-calcified and low-attenuation plaques confer a higher risk of instability and rupture.[22,23] Against this background, the relative absence of macrocalcification in non-diabetic patients with ED may identify a subgroup with more active, inflammation-driven, and potentially higher-risk plaque biology despite comparable angiographic disease severity.

These findings may have practical clinical implications. Contemporary trials support conservative management strategies in stable CAD,[24,25] yet the ability to identify patients who harbour predominantly non-calcified and potentially vulnerable plaques remains limited in routine practice. Endothelial function testing – simple, non-invasive, and easily repeatable – may offer a complementary tool for refining risk stratification in non-diabetic patients with CAD. Such individuals with ED could represent candidates for intensified diagnostic assessment, including coronary computed tomography angiography, which is particularly sensitive for detecting non-macro calcified plaque features. Furthermore, this phenotype may benefit from more aggressive preventive measures, including tighter LDL-C lowering or anti-inflammatory strategies, given the biologically active nature of non-calcified atherosclerosis.

In summary, our data support the concept of two divergent atherosclerotic phenotypes in non-diabetic CAD: (1) a calcific–metabolic phenotype characterized by preserved endothelial function, and (2) a non-calcified, ED-driven phenotype potentially reflecting heightened inflammatory activity. Future imaging and mechanistic studies are warranted to clarify the determinants of these patterns and to determine whether integrating endothelial function into clinical decision-making can improve patient outcomes.

Limitations

This study has several limitations. It was a single-center analysis with a relatively small sample size, which may limit generalizability. Endothelial function was measured peripherally using EndoPAT, which may not fully reflect coronary endothelial physiology. Finally, the cross-sectional design precludes causal inference despite multivariable adjustment.

Conclusion

In non-diabetic patients with coronary artery disease, endothelial dysfunction was associated with a significantly lower prevalence of coronary macrocalcification. This finding supports the existence of distinct atherosclerotic phenotypes and suggests that endothelial function assessment may aid in refining cardiovascular risk stratification beyond traditional factors in the era of data supporting conservative treatment of stable CAD.

Conflict of interest
The authors have no relevant financial or non-financial interests to disclose.

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Ethical statement
The study was conducted in accordance with the Declaration of Helsinki.

Informed consent
Written informed consent was obtained from all individual participants included in the study.

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