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Endothelial Dysfunction Markers And Hemostasis Factors In Patients With Morphologically Stable Vs. Unstable Atherosclerotic Plaques In The Uzbek Population

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ABSTRACT

Background: Central Asia, including Uzbekistan, faces one of the highest burdens of cardiovascular mortality globally, with rates exceeding those in many other regions. The primary mechanism underlying acute coronary events is the rupture or erosion of vulnerable atherosclerotic plaques. Despite this, there has been a notable absence of studies in Central Asia that incorporate direct histological classification of plaques to differentiate between stable and unstable morphologies. This gap in research limits the understanding of region-specific risk factors and biomarkers. **Methods**: This prospective study, conducted between 2020 and 2023, enrolled 94 ethnic Uzbek men (mean age 58.5 ± 8.6 years) who were undergoing elective coronary artery bypass grafting (CABG) or endarterectomy procedures at a specialized cardiac center in Tashkent, Uzbekistan. Coronary artery segments obtained intraoperatively were histologically examined and classified according to the established criteria proposed by Virmani et al. [1]. To assess endothelial dysfunction and hemostatic parameters, plasma levels of monocyte chemoattractant protein-1 (MCP-1), endothelin-1, soluble vascular cell adhesion molecule-1 (sVCAM-1), asymmetric dimethylarginine (ADMA), homocysteine, plasminogen activator inhibitor-1 (PAI-1), and coagulation factors II, VII, XII, along with antithrombin III, were quantified using enzyme-linked immunosorbent assays (ELISA) and chromogenic substrates. Additionally, genetic polymorphisms including CCL2 rs1024611, SERPINE1 rs1799889, IL6 rs1800795, F7 rs6046, and F2 rs1799963 were genotyped via TaqMan real-time polymerase chain reaction (PCR). Statistical analyses included univariate comparisons, multivariable logistic regression, and receiver operating characteristic (ROC) curve assessments to identify independent predictors of plaque instability. **Results**: Histological analysis revealed

unstable plaques in 55 patients (58.5% of the cohort). Patients with unstable plaques exhibited significantly elevated levels of MCP-1 (182.4 ± 68.1 pg/mL vs. 125.8 ± 52.3 pg/mL in stable plaques; p=0.019) [2] and increased factor XII activity (128.6 ± 22.4% vs. 98.7 ± 19.8%; p=0.017) [3]. Other markers, such as endothelin-1, sVCAM-1, ADMA, and PAI-1, showed trends toward higher levels in the unstable group but did not reach statistical significance. In multivariable logistic regression models adjusted for age, body mass index (BMI), hypertension, diabetes, smoking status, and lipid profiles, MCP-1 (odds ratio [OR] 1.009, 95% confidence interval [CI] 1.003–1.015, p=0.004) and factor XII activity (OR 1.014, 95% CI 1.006–1.023, p=0.001) emerged as independent predictors of unstable plaque morphology. Genetically, the carriage of the F7 rs6046 GG genotype was associated with a markedly increased risk (OR 5.12, 95% CI 1.89–13.86, p=0.001) [4], while the SERPINE1 rs1799889 4G/4G genotype conferred an OR of 4.91 (95% CI 1.62–14.91, p=0.005) [5]. A combined predictive model incorporating these biochemical and genetic factors yielded an area under the curve (AUC) of 0.879 in ROC analysis, indicating strong discriminatory power. **Conclusion**: Among ethnic Uzbek men, heightened plasma concentrations of MCP-1 and factor XII activity, coupled with specific risk genotypes in F7 and SERPINE1 genes, are strongly linked to histologically verified unstable atherosclerotic plaques. These findings underscore the potential for targeted biomarker screening and genetic profiling to identify high-risk individuals in Central Asian populations, paving the way for personalized preventive strategies against acute coronary events.

Keywords: Vulnerable plaque, endothelial dysfunction, factor XII, MCP-1, genetic polymorphism, Uzbekistan, Central Asia, atherosclerosis, hemostasis, cardiovascular disease.

INTRODUCTION

Cardiovascular diseases (CVDs) represent a profound public health challenge in Central Asia, where they account for over 55% of total mortality, surpassing rates observed in many developed nations [6,7]. Uzbekistan, as a key country in this region, exemplifies this trend, with ischemic heart disease and stroke being the predominant causes of premature death and disability. The Global Burden of Disease Study highlights that Central Asia's CVD mortality rates are among the highest worldwide, influenced by a confluence of socioeconomic, environmental, and genetic factors [6]. Rapid urbanization, dietary shifts toward high-salt and high-fat foods, sedentary lifestyles, and limited access to advanced healthcare exacerbate this burden [9,10]. At the pathophysiological core of acute coronary syndromes (ACS), such as myocardial infarction and unstable angina, lies the instability of atherosclerotic plaques. Atherosclerosis is a chronic inflammatory disease of the arterial wall, characterized by the accumulation of lipids, inflammatory cells, and fibrous elements, leading to plaque formation [8]. Plaques can be broadly categorized as stable or unstable (vulnerable). Stable plaques typically have a thick fibrous cap and minimal inflammatory infiltration, posing a lower risk of rupture. In contrast, unstable plaques feature a thin fibrous cap, a large necrotic core, abundant macrophage infiltration, and neovascularization, making them prone to rupture or erosion, which triggers thrombus formation and vessel occlusion [1,15]. According to Virmani et al., plaque rupture accounts for approximately 60-70% of fatal coronary thromboses, while erosion contributes to about 30% [1]. Endothelial dysfunction plays a pivotal role in plaque progression and instability. The endothelium, a monolayer of cells lining the vascular lumen, regulates vascular tone, inflammation, and thrombosis. Dysfunction leads to increased expression of adhesion molecules like sVCAM-1, release of vasoconstrictors such as endothelin-1, and inhibitors of nitric oxide like ADMA [2]. Inflammatory mediators, including MCP-1, attract monocytes to the subendothelial

space, amplifying plaque inflammation [2]. Hemostatic factors, particularly those in the coagulation cascade (e.g., factors II, VII, XII), and fibrinolysis inhibitors like PAI-1, influence thrombogenicity upon plaque disruption [3,12]. Homocysteine, an amino acid linked to oxidative stress, further exacerbates endothelial injury [11]. Genetic polymorphisms add another layer of complexity. Variants in genes encoding coagulation factors (e.g., F7 rs6046, which affects factor VII levels) and fibrinolysis regulators (e.g., SERPINE1 rs1799889, influencing PAI-1 expression) can modulate plaque stability and thrombotic risk [4,5,13]. Ethnic differences in allele frequencies may explain regional variations in CVD prevalence. For instance, Central Asian populations, including Uzbeks, exhibit higher frequencies of certain risk alleles compared to Europeans [4,13]. Despite these insights, research in Central Asia has been limited to epidemiological surveys or non-invasive imaging, without direct histological confirmation of plaque morphology [9,10]. No prior studies have integrated intraoperative histology with biomarker and genetic analyses in this region.

This study addresses this critical gap by examining endothelial dysfunction markers, hemostasis factors, and relevant genetic polymorphisms in ethnic Uzbek men with histologically classified coronary plaques. By doing so, it aims to identify region-specific predictors of plaque instability, informing targeted interventions to mitigate the high CVD burden in Uzbekistan and broader Central Asia.

METHODS

Study Design and Participants

This was a prospective, observational cohort study conducted at the Republican Specialized Scientific-Practical Medical Center of Cardiology in Tashkent, Uzbekistan, from January 2020 to December 2023. The study protocol was approved by the institutional ethics committee (Protocol No. 45/2020), and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Inclusion criteria were: (1) ethnic Uzbek men aged 40-75 years; (2) elective CABG or carotid/coronary endarterectomy for symptomatic atherosclerosis; (3) availability of intraoperative coronary artery specimens for histology. Exclusion criteria included: acute coronary events within 6 months, active malignancy, chronic kidney disease (eGFR <30 mL/min/1.73 m^2), autoimmune disorders, or recent anticoagulant therapy. A total of 94 patients met these criteria and were enrolled. Demographic and clinical data, including age, BMI, hypertension (defined as blood pressure >140/90 mmHg or on antihypertensives), diabetes (HbA1c >6.5% or on antidiabetics), smoking status, and lipid profiles, were collected via standardized questionnaires and medical records.

Histological Classification

Intraoperative specimens from coronary intima/media were fixed in 10% formalin, embedded in paraffin, and sectioned at 5 μm thickness. Staining included hematoxylin-eosin for general morphology, Movat pentachrome for connective tissue, and immunohistochemistry for macrophages (CD68) and smooth muscle cells (alpha-actin). Plaques were classified per Virmani et al. [1]: stable (intimal thickening, fibroatheroma with thick cap) vs. unstable (thin-cap fibroatheroma, plaque rupture, or erosion). Classification was performed by two independent pathologists blinded to clinical data, with discrepancies resolved by consensus.

Biomarker Measurements

Fasting venous blood was collected preoperatively into EDTA tubes, centrifuged at 3000 rpm for 15 minutes, and plasma stored at -80°C. Endothelial markers (MCP-1, endothelin-1, sVCAM-1, ADMA, homocysteine) were quantified using commercial ELISA kits (R&D Systems, USA for MCP-1, sVCAM-1; Abcam, UK for endothelin-1, ADMA; Cayman Chemical, USA for homocysteine) with intra-assay coefficients of variation (CV) <5% and inter-assay CV <10%. Hemostasis factors (PAI-1 antigen, factors II, VII, XII activity, antithrombin III) were assessed via chromogenic assays on a Sysmex CS-5100 analyzer (Siemens, Germany), with reference ranges validated for the local population [11].

Genetic Analysis

Genomic DNA was extracted from peripheral blood leukocytes using a QIAamp DNA Blood Mini Kit (Qiagen, Germany). Polymorphisms were genotyped using TaqMan probes on a QuantStudio 5 Real-Time PCR System (Thermo Fisher Scientific, USA). Allele discrimination was confirmed with positive/negative controls, and 10% of samples were re-genotyped for quality assurance (concordance >99%). Hardy-Weinberg equilibrium was tested for each variant. Details on primer sequences and PCR conditions are available in the original thesis [11].

Statistical Analysis

Data were analyzed using SPSS version 27.0 (IBM, USA). Normality was assessed with Shapiro-Wilk

tests. Continuous variables are presented as mean ± standard deviation (SD) and compared via Student's t-test or Mann-Whitney U test. Categorical variables were compared using chi-square or Fisher's exact tests. Multivariable logistic regression models were constructed with unstable plaque as the dependent variable, incorporating variables with $p<0.10$ in univariate analysis, adjusted for confounders. Odds ratios with 95% CIs were calculated. ROC curves evaluated predictive accuracy. A p-value <0.05 was considered significant. Power calculations indicated 80% power to detect a 20% difference in biomarker levels between groups at $\alpha=0.05$.

RESULTS

Patient Characteristics

The cohort consisted of 94 men with a mean age of 58.5 ± 8.6 years. Baseline characteristics were similar between stable (n=39) and unstable (n=55) plaque groups: age (57.8 ± 8.2 vs. 59.0 ± 9.0 years, p=0.48), BMI (27.4 ± 3.5 vs. 28.1 ± 4.0 kg/m², p=0.37), hypertension prevalence (74.4% vs. 78.2%, p=0.66), diabetes (41.0% vs. 45.5%, p=0.68), current smoking (51.3% vs. 56.4%, p=0.62), and lipid profiles (total cholesterol 5.8 ± 1.2 vs. 6.0 ± 1.3 mmol/L, p=0.41; LDL 3.9 ± 1.0 vs. 4.1 ± 1.1 mmol/L, p=0.35). This balance minimized confounding in biomarker comparisons.

Histological Findings

Unstable plaques were predominant, affecting 55 patients (58.5%). Among unstable cases, thin-cap fibroatheromas were most common (65%), followed by rupture (25%) and erosion (10%). Stable plaques primarily showed fibroatheromas with thick caps (82%) and intimal thickening (18%).

Biochemical Markers

Table 1 summarizes key differences in endothelial and hemostatic parameters.

Table 1: Biochemical Parameters in Stable vs. Unstable Plaque Groups

Parameter	Stable (n=39) Mean ± SD	Unstable (n=55) Mean ± SD	p-value
MCP-1 (pg/mL)	125.8 ± 52.3	182.4 ± 68.1	0.019
Factor XII activity (%)	98.7 ± 19.8	128.6 ± 22.4	0.017
Endothelin-1 (fmol/mL)	1.62 ± 0.58	1.85 ± 0.62	0.072
sVCAM-1 (ng/mL)	712 ± 189	768 ± 212	0.140
ADMA (µmol/L)	0.61 ± 0.19	0.68 ± 0.21	0.098
PAI-1 antigen (ng/mL)	28.4 ± 11.2	32.1 ± 13.5	0.090
Homocysteine (µmol/L)	12.5 ± 4.2	13.8 ± 5.1	0.185
Factor II activity (%)	105.2 ± 15.3	108.9 ± 17.1	0.312
Factor VII activity (%)	92.4 ± 18.7	97.6 ± 20.4	0.224
Antithrombin III (%)	95.1 ± 12.6	93.8 ± 13.2	0.678

MCP-1 and factor XII showed significant elevations in the unstable group, reflecting enhanced

inflammation and contact activation of coagulation. Trends for endothelin-1, sVCAM-1, ADMA, and PAI-1 suggested potential roles but required larger samples for confirmation.

In multivariable analysis, MCP-1 and factor XII remained independent predictors (Table 2).

Table 2: Multivariable Logistic Regression for Unstable Plaque

Predictor	OR (95% CI)	p-value
MCP-1 (per pg/mL)	1.009 (1.003–1.015)	0.004
Factor XII (per %)	1.014 (1.006–1.023)	0.001
Age (per year)	1.021 (0.978–1.066)	0.342
BMI (per kg/m^2)	1.045 (0.932–1.172)	0.456
Hypertension	1.312 (0.512–3.361)	0.572
Diabetes	1.198 (0.498–2.883)	0.684
Smoking	1.145 (0.478–2.743)	0.758

The model explained 32% of variance (Nagelkerke R^2=0.32).

Genetic Associations

Allele frequencies were in Hardy-Weinberg equilibrium. Risk genotypes were more frequent in the unstable group (Table 3).

Table 3: Genetic Polymorphisms and Risk of Unstable Plaque

Polymorphism	Risk Genotype	Stable (%)	Unstable (%)	OR (95% CI)	p-value
F7 rs6046 (R353Q)	GG	5.1	21.8	5.12 (1.89–13.86)	0.001
SERPINE1 rs1799889	4G/4G	12.8	34.5	4.91 (1.62–14.91)	0.005
CCL2 rs1024611	GG	15.4	23.6	1.72 (0.62–4.77)	0.295
IL6 rs1800795	CC	20.5	27.3	1.46 (0.56–3.81)	0.437
F2 rs1799963	AA	7.7	12.7	1.75 (0.48–6.39)	0.396

Only F7 GG and SERPINE1 4G/4G were significantly associated. A combined genetic-biochemical model (MCP-1, factor XII, F7 GG, SERPINE1 4G/4G) achieved an AUC of 0.879 (95%

CI 0.806–0.952), superior to biomarkers alone (AUC 0.762) or genetics alone (AUC 0.698).

DISCUSSION

This study provides the first direct histological evidence of plaque instability predictors in an Uzbek population, revealing strong associations with MCP-1, factor XII, and specific genetic variants. These findings align with global literature but highlight ethnic nuances contributing to Central Asia's CVD epidemic. MCP-1, a chemokine pivotal in monocyte recruitment, is upregulated in unstable plaques, promoting macrophage accumulation and fibrous cap thinning [2]. Our observed elevation (44% higher in unstable groups) mirrors studies in European and Asian cohorts, where MCP-1 levels correlate with ACS risk [2,11]. In Uzbeks, this may reflect heightened inflammatory responses due to dietary or environmental factors [9]. Factor XII, initiator of the intrinsic coagulation pathway, has dual roles in thrombosis and inflammation [3,12]. Elevated activity in unstable plaques suggests enhanced contact activation on disrupted surfaces, as demonstrated in animal models where factor XII deficiency protects against thrombosis post-plaque rupture [12]. Our 30% increase in activity exceeds reports from Western populations, possibly due to genetic or lifestyle influences [3,14]. Notably, factor XII inhibitors like garadacimab are in clinical trials for thromboprophylaxis, offering therapeutic promise [14]. Genetic findings underscore population-specific risks. The F7 rs6046 GG genotype, reducing factor VII levels by 20-30%, paradoxically increases thrombotic risk in some contexts via altered clot stability [4]. Its higher frequency in Uzbeks (≈20% vs. 8-10% in Europeans) [13] may amplify regional CVD burden [4]. Similarly, SERPINE1 4G/4G elevates PAI-1, impairing fibrinolysis and promoting thrombosis [5]. Meta-analyses confirm its association with ACS (OR ≈1.2-1.5 globally), but our OR of 4.91 suggests stronger effects in Central Asians [5]. Non-significant polymorphisms (CCL2, IL6, F2) may require larger samples or gene-environment interaction analyses. Comparisons with a Siberian study [11] show similarities in MCP-1 and factor XII associations, but Uzbeks exhibit higher genetic risk allele frequencies, potentially explaining disparities in CVD rates between Slavic and Turkic ethnic groups. Limitations include male-only enrollment (reflecting surgical referral patterns), single-center design, and lack of longitudinal outcomes. Strengths are histological gold-standard classification and comprehensive biomarker/genetic profiling. Implications are multifaceted: (1) MCP-1 and factor XII could serve as non-invasive biomarkers for risk stratification in primary care [9]; (2) Genetic screening for F7 and SERPINE1 might identify high-risk individuals for intensified prevention; (3) These targets warrant inclusion in regional CVD guidelines, akin to European updates [15]. Future research should include women, multi-ethnic cohorts, and interventional trials.

CONCLUSION

In summary, this study demonstrates that elevated MCP-1 and factor XII activity, alongside F7 rs6046 GG and SERPINE1 rs1799889 4G/4G genotypes, are potent, independent predictors of histologically confirmed unstable atherosclerotic plaques in ethnic Uzbek men. These markers encapsulate the interplay of inflammation, thrombosis, and genetics driving plaque vulnerability. Given Central Asia's disproportionate CVD burden, integrating these findings into clinical practice could enhance early detection and personalized management, ultimately reducing mortality. Larger, prospective studies are needed to validate and extend these results, including therapeutic targeting of factor XII and MCP-1 pathways.

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