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CLINICAL, INSTRUMENTAL AND MOLECULAR-GENETIC CHARACTERISTICS OF PATIENTS WITH CHRONIC VENOUS INSUFFICIENCY OF THE LOWER EXTREMITIES AND THE ROLE OF THE MMP9 GLN279ARG POLYMORPHISM IN VENOUS WALL REMODELING

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Abstract

Background. Chronic venous insufficiency (CVI) of the lower extremities is one of the most prevalent disorders of the human vascular system and a leading cause of disability among the working-age population. Matrix metalloproteinase 9 (MMP9) is a key effector of extracellular matrix degradation and venous wall remodeling, and the functional Gln279Arg (rs17576) polymorphism may modify individual susceptibility to the disease.

Aim. To characterize the clinical, laboratory and ultrasonographic features of patients with CVI and to evaluate the association of the MMP9 Gln279Arg polymorphism with the risk of developing and progressing CVI in an ethnically defined cohort from the Fergana Valley of Uzbekistan.

Materials and methods. A case-control study included 98 patients with CVI (CEAP classes C3-C6) and 87 healthy controls of comparable age and sex. All participants underwent clinical examination, coagulation testing and duplex Doppler ultrasonography. The MMP9 Gln279Arg polymorphism was genotyped by polymerase chain reaction. Associations were assessed using the Pearson chi-square test and odds ratios (OR) with 95% confidence intervals (CI).

Results. Telangiectasia (92%), limb oedema (87%), trophic skin lesions (77%) and varicose superficial veins (77%) dominated the clinical picture, while healed and active venous ulcers were present in 45% and 16% of patients, respectively. A tendency to hypercoagulation was observed, more pronounced in C5-C6 patients. Combined vertical and horizontal pathological refluxes were the leading ultrasonographic finding (38.7%). The unfavorable Arg allele (OR=1.3; 95% CI 0.82-1.95) and the Arg/Arg genotype (OR=1.3; 95% CI 0.59-3.08) were more frequent in patients; in the severe C5-C6 subgroup the Gln/Arg and Arg/Arg genotypes reached OR=1.2 and OR=1.4, respectively, whereas the Gln/Gln genotype showed a protective tendency (OR=0.7-0.8).

Conclusion. The Gln279Arg polymorphism of the MMP9 gene contributes to venous wall remodeling and progressive valvular incompetence. The unfavorable Arg allele and

Arg/Arg genotype are candidate predictors of CVI development and progression and may support a personalized, genetically informed preventive strategy.

Keywords: Chronic venous insufficiency; MMP9; Gln279Arg; rs17576; matrix metalloproteinase; venous wall remodeling; CEAP; genetic predictor.

1. Introduction

Chronic venous insufficiency (CVI) of the lower extremities is among the most widespread disorders of the human vascular system. Despite considerable advances in the diagnosis and treatment of chronic venous pathology, CVI remains an important medico-social problem: its prevalence, the particular features of its clinical course and recurrence, and its outcomes lead to a substantial reduction in patients' quality of life across all age categories. Severe complications such as pulmonary embolism and venous trophic ulcers represent some of the gravest consequences of advanced disease, and the socio-economic burden is driven by the cost of diagnosis and treatment, the psycho-emotional impact on patients and the persistent role of CVI as a major cause of disability among the working-age population worldwide.

Chronic venous disorders affect a substantial proportion of adults in the United States, Europe and Asia, with women disproportionately represented. Pooled epidemiological analyses confirm both a high global prevalence and a continuing rise in advanced forms, with an annual increase in the number of patients presenting with venous trophic ulcers [1]. The clinical heterogeneity of the disease is captured by the Clinical-Etiological-Anatomical-Pathophysiological (CEAP) classification, updated in 2020, in which classes C3 to C6 denote progressively severe CVI, ranging from oedema and skin changes to healed and active venous ulcers [2]. In the cohort studied here, the predominance of advanced CEAP classes underscores the clinical relevance of identifying patients at risk of progression.

The pathogenesis of CVI is multifactorial and incompletely understood. Reduced shear stress caused by venous stasis and retrograde flow induces an inflammatory, prothrombotic endothelial phenotype; leukocyte-endothelial interactions, infiltration of monocytes and macrophages, and the release of cytokines and growth factors drive the remodeling of the venous wall and valves. A central molecular event is the remodeling of the extracellular matrix (ECM), governed by the balance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) [3, 4]. Several studies have demonstrated increased expression of MMP-1, MMP-2, MMP-3, MMP-7 and MMP-9, together with TIMP-1 and TIMP-3, in the varicose vein wall compared with normal vein, and ex vivo models of venous hypertension show that mechanically loaded venous segments increase MMP expression while reducing wall contractility [5].

Matrix metalloproteinase 9 (MMP9, gelatinase B) is a zinc-dependent endopeptidase that degrades denatured collagen, basement membrane components and other structural elements of the ECM in the venous wall under pathological conditions. It is abundantly stored in neutrophil granules and plays a leading role in leukocyte recruitment to sites of inflammation and tissue injury [6]. The structure and function of the venous wall are partly regulated by MMPs, whose expression is modulated by venous hydrostatic pressure, hypoxia and inflammatory reactions; MMPs can both initiate wall remodeling through proteolytic cleavage of ECM components and influence the proliferation, apoptosis and migration of medial smooth-muscle cells [7]. MMP9 has been shown to be present immediately after the formation of trophic ulcers, and its activity is closely linked to the destruction of the ECM and the development of non-healing venous ulcers.

The MMP9 gene is located on the long arm of chromosome 20 at locus 20q13.12. The Gln279Arg (rs17576) polymorphism corresponds to a single-nucleotide substitution replacing glutamine (Gln) with arginine (Arg) at position 279. Because any change in MMP9 activity may alter venous structure, promote venous dilatation and contribute to the symptoms of CVI, this functional variant is a plausible candidate predictor of disease susceptibility [4, 8]. However, the reported associations of MMP9 variants with chronic venous disease (CVD) are inconsistent and at times contradictory, reflecting the ethnic heterogeneity of the studied samples and population differences in the frequencies of allelic and genotypic variants [9, 10]. To date, no definitive combination of genetic polymorphisms has been established as a reliable predictor of CVI in the population of Uzbekistan.

Accordingly, the aim of the present study was twofold: to characterize the clinical, laboratory and ultrasonographic features of patients with CVI of the lower extremities, and to evaluate the contribution of the MMP9 Gln279Arg polymorphism to the risk of developing and progressing CVI in an ethnically defined cohort from the Fergana Valley of Uzbekistan, thereby providing a basis for genetically informed prediction and prevention.

2. Materials and Methods

2.1. Study Design and Participants

A case-control study was conducted between 2020 and 2022 at the clinics of the Andijan State Medical Institute and the Andijan regional branch of the Republican Scientific Centre of Emergency Medical Care. The main group comprised 98 patients with previously diagnosed CVI who were permanent residents of the Fergana Valley of Uzbekistan. According to the 2020 CEAP classification, patients were divided into two subgroups: 45 patients with CVI of moderate severity (CEAP classes C3-C4) and 53 patients with severe CVI (CEAP classes C5-C6).

The control group included 87 conventionally healthy individuals without clinical manifestations of CVI at the time of examination and without a personal or family history of venous disease; they comprised in-patients treated for unrelated conditions and

volunteers. The groups were comparable in age and sex (p>0.05). Women predominated in the cohort (71 patients, 72.5%), and patients aged 46-55 years constituted the largest age group (41 patients, 41.8%); the mean age of patients was 62.7 +/- 1.3 years. The disease duration was 5.6 +/- 4.1 years in C3-C4 patients and 11.8 +/- 4.6 years in C5-C6 patients.
Inclusion criteria were clinical manifestations corresponding to CEAP classes C3-C6 and age over 18 years. Exclusion criteria were CEAP classes C0-C2, oncological or endocrine disease, laboratory-confirmed diabetes mellitus, decompensated chronic disease of internal organs, pregnancy or lactation, and acute infectious disease. Informed consent was obtained from every participant, and each was informed of the design and objectives of the study.

2.2. Clinical, Laboratory and Instrumental Methods

The diagnosis of CVI was verified according to the CEAP 2020 criteria on the basis of clinical, laboratory-instrumental and molecular-genetic findings. Beyond the assessment of complaints and inspection, the circumference of the foot, ankle and leg was measured to objectify oedema; a clinically significant difference of at least 1.5 cm relative to the healthy limb was used as the threshold. The coagulation profile was characterized by the activated partial thromboplastin time, the prothrombin index (Quick method), the thrombotest (Fuente Ita), the plasma fibrinogen concentration (Rutberg), the international normalized ratio and the clotting time (Sukharev).
Duplex Doppler ultrasonography of the deep and superficial veins of the lower extremities was performed in horizontal and vertical positions with the use of loading tests (compression test and Valsalva manoeuvre), using an expert-class ultrasound system with an 8-12 MHz linear transducer. B-mode was used to study venous anatomy, and colour Doppler mapping was used to assess flow velocity. The examination evaluated venous patency, wall integrity, valve competence and the presence and direction of pathological reflux in the supine and upright positions.

2.3. Molecular-Genetic Methods

Genomic DNA was extracted from peripheral blood lymphocytes. Five millilitres of venous blood were collected into EDTA vacutainers and stored at -70 degrees Celsius. DNA was isolated using a commercial extraction kit, and a modified phenol-chloroform extraction method was applied where required. The concentration and purity of the extracted DNA were measured spectrophotometrically at A260/280; a ratio of 1.7-1.8 confirmed low protein contamination and suitability for amplification without additional purification. The MMP9 Gln279Arg (rs17576) polymorphism was genotyped by polymerase chain reaction using standard commercial detection kits and validated thermal-cycling protocols, with electrophoretic verification of amplification products where necessary. Genetic analysis followed the GRIPS recommendations to enhance the transparency and quality of risk prediction.

2.4. Statistical Analysis

Statistical analysis was performed with Statistica 10.0 and the OpenEpi v2.3 software package. Conformity of genotype distributions to the Hardy-Weinberg equilibrium was tested using the GenePop online program; allele frequencies, observed and expected heterozygosity, and the fixation index were calculated using standard population-genetic formulae. Allele and genotype frequencies were compared between groups using the Pearson chi-square test, with the Yates correction for continuity applied to 2x2 tables when the expected count in any cell was five or fewer. The strength of association was expressed as the odds ratio (OR) with a 95% confidence interval (CI): OR=1 indicated absence of association, OR>1 was interpreted as an increased-risk factor, and OR<1 as a protective factor.

3. Results

3.1. Clinical and Laboratory Findings

Clinically significant manifestations of CVI - telangiectasia, nocturnal muscle cramps, and oedema of the feet, ankles and legs not resolving after short rest - were observed in 74 patients (75.5%). The left lower limb was most frequently affected, in 73.6% of C3-C4 patients and 79.4% of C5-C6 patients. The clinical picture corresponded fully to the symptomatology of the respective CEAP classes and progressed with increasing disease duration; the principal manifestations, in addition to varicose transformation of the superficial veins and oedema, were extensive trophic disorders involving a large part of the leg.

Analysis of the local status showed that trophic skin lesions of the lower extremities with partial involvement of the superficial veins were present in 77% of patients. Almost half of the patients had a healed venous leg ulcer (45%) and approximately one sixth had an active ulcer (16%) requiring in-patient treatment. Skin manifestations were almost ubiquitous: telangiectasia in 92%, trophic skin lesions in 77% and oedema of the subcutaneous tissue of affected zones in 87% (Figure 1, Table 1). Single trophic ulcers were observed in 29 (55.1%) of the C5-C6 patients, of whom 38% had varicose disease and 62% post-thrombophlebitic disease; in 67.2% of patients the ulcer area did not exceed 5 square centimetres.

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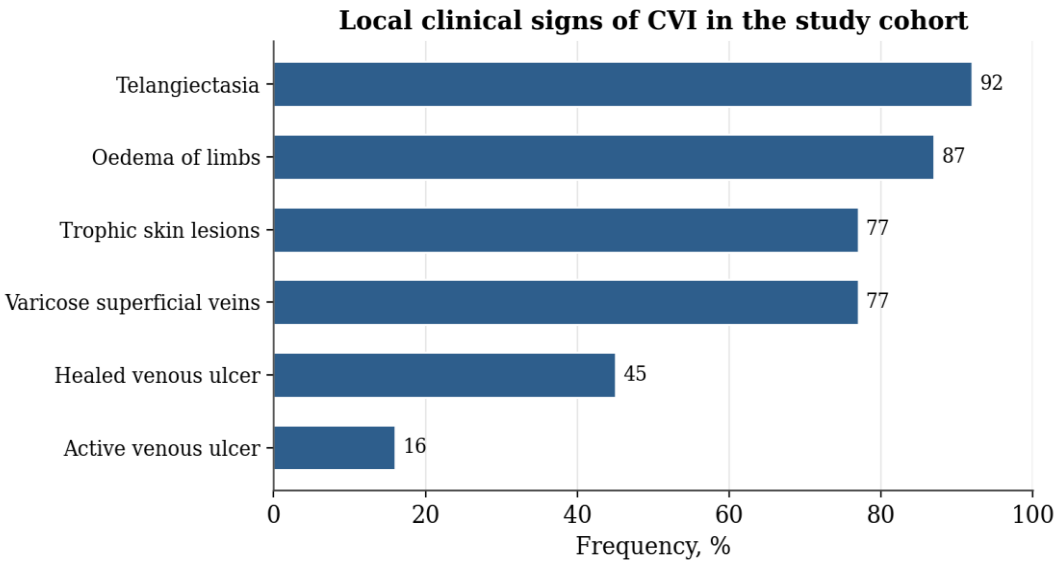

Figure 1. Frequency of local clinical signs of chronic venous insufficiency in the study cohort (% of patients).

Table 1. Local clinical signs of chronic venous insufficiency in the study cohort

Type of change	CVI patients (%)	Healthy controls (%)
Skin trophic lesions of the lower extremities	77	not detected
Varicose changes of superficial veins	77	not detected
Healed venous leg ulcer	45	not detected
Active venous leg ulcer	16	not detected
Telangiectasia of affected skin zones	92	not detected
Oedema of the lower extremities	87	not detected

Coagulation indices in the main and control groups were comparable on admission and did not differ significantly ($p>0.05$). Nevertheless, all patients showed a tendency to hypercoagulation, despite the prior use of anticoagulants in some, and this tendency was more pronounced in the C5-C6 subgroup. Plasma fibrinogen (Rutberg) in patients with severe forms was approximately 15% higher than in those with moderate forms, whereas the international normalized ratio, thrombotest and clotting time did not differ substantially between subgroups.

3.2. Ultrasonographic Findings

Arterial flow in patients did not differ substantially from that of healthy individuals, whereas a marked reduction of linear blood-flow velocities along the main veins was observed. Haemodynamic disturbances of the deep venous system predominated, with lumen dilatation, dilatation of all layers of the venous wall, and incompetence of the ostial

and perforator valves. Combined vertical and horizontal pathological refluxes were the leading pattern, detected in 38.7% of patients, followed by horizontal reflux through incompetent perforator valves in 22.5% (Figure 2, Table 2). More than a quarter of cases showed sapheno-popliteal valve incompetence with vertical reflux (17.3%), combined sapheno-femoral and sapheno-popliteal incompetence accounted for 16.4%, and isolated sapheno-femoral incompetence was the least frequent (5.1%).

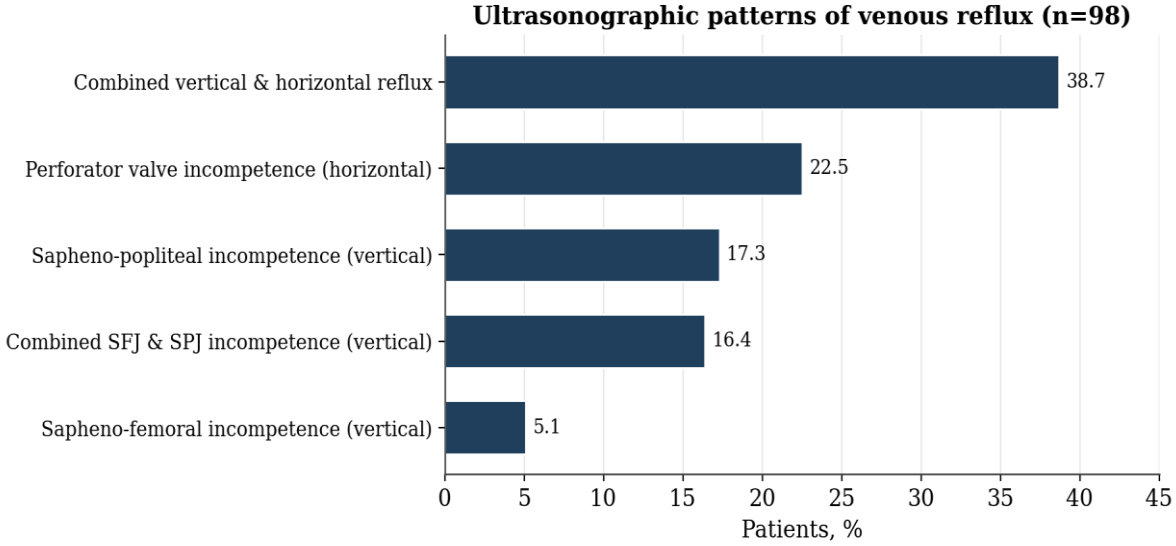

Figure 2. Distribution of ultrasonographic patterns of venous reflux among patients (% of n=98).

Table 2. Ultrasonographic patterns of chronic venous insufficiency in patients (n=98)

Ultrasonographic pattern	**n**	**%**
Sapheno-femoral valve incompetence with vertical reflux	5	5.1
Sapheno-popliteal valve incompetence with vertical reflux	17	17.3
Combined sapheno-femoral and sapheno-popliteal incompetence	16	16.4
Perforator valve incompetence with horizontal reflux	22	22.5
Combined vertical and horizontal pathological refluxes	38	38.7
Total	**98**	**100**

In the decompensated stage, significant haemodynamic disturbances of venous outflow were recorded, consisting of reduced linear and volumetric flow through the superficial and deep venous systems and a compensatory increase in outflow through the muscular and subcutaneous collateral system, which carried up to 47.5% of the venous blood in severe forms. These instrumental findings paralleled the clinical changes and confirmed the predominance of advanced CEAP classes (C4-C6) in the cohort; notably, the spectrum of

abnormal ultrasonographic findings generally exceeded the extent of the clinical manifestations.

3.3. MMP9 Gln279Arg Polymorphism

The observed genotype distributions of the Gln279Arg polymorphism conformed to the Hardy-Weinberg equilibrium in both the patient and control groups. The frequencies of the major Gln and minor Arg alleles were 0.64/0.36 in the main group and 0.69/0.31 in controls. The favourable homozygous Gln/Gln genotype, denoting normal enzyme activity, was slightly less frequent in patients, whereas the unfavorable homozygous Arg/Arg genotype, denoting reduced enzyme activity, was more frequent in patients than in controls (16.3% vs 12.6%). Relative deviation of observed from expected heterozygosity was negative in both groups (D = -0.14), with a high level of heterozygosity at this locus (Figure 3).

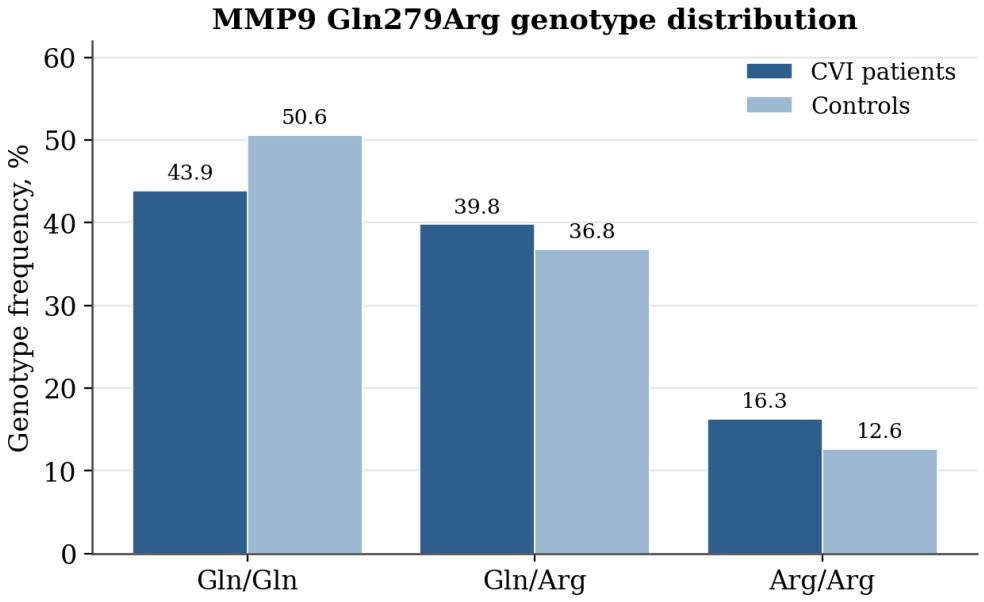

Figure 3. Distribution of MMP9 Gln279Arg genotypes in patients with CVI (n=98) and controls (n=87).

Association analysis showed a tendency towards a higher frequency of the unfavorable Arg allele in patients (OR=1.3; 95% CI 0.82-1.95), while the Gln allele was not associated with disease (OR=0.8; 95% CI 0.51-1.22). The favourable Gln/Gln genotype was less frequent in patients (43.9% vs 50.6%; OR=0.8; 95% CI 0.43-1.36), the heterozygous Gln/Arg genotype was marginally more frequent (39.8% vs 36.8%; OR=1.1; 95% CI 0.63-2.06), and the Arg/Arg genotype reached OR=1.3 (95% CI 0.59-3.08) (Table 3, Figure 4).

Table 3. Distribution and association of the MMP9 Gln279Arg polymorphism in patients and controls

Group	Allele / Genotype	Patients, %	Controls, %	OR (95% CI)
Main group (n=98)	Arg allele	36.2	31.0	1.3 (0.82-1.95)
	Gln/Gln	43.9	50.6	0.8 (0.43-1.36)
	Gln/Arg	39.8	36.8	1.1 (0.63-2.06)
	Arg/Arg	16.3	12.6	1.3 (0.59-3.08)
CVI C5-C6 (n=53)	Gln/Arg	41.5	36.8	1.2 (0.61-2.45)
	Arg/Arg	17.0	12.6	1.4 (0.54-3.67)

OR - odds ratio; CI - confidence interval. The Gln/Gln genotype showed a protective tendency in severe disease (OR=0.7; 95% CI 0.35-1.38).

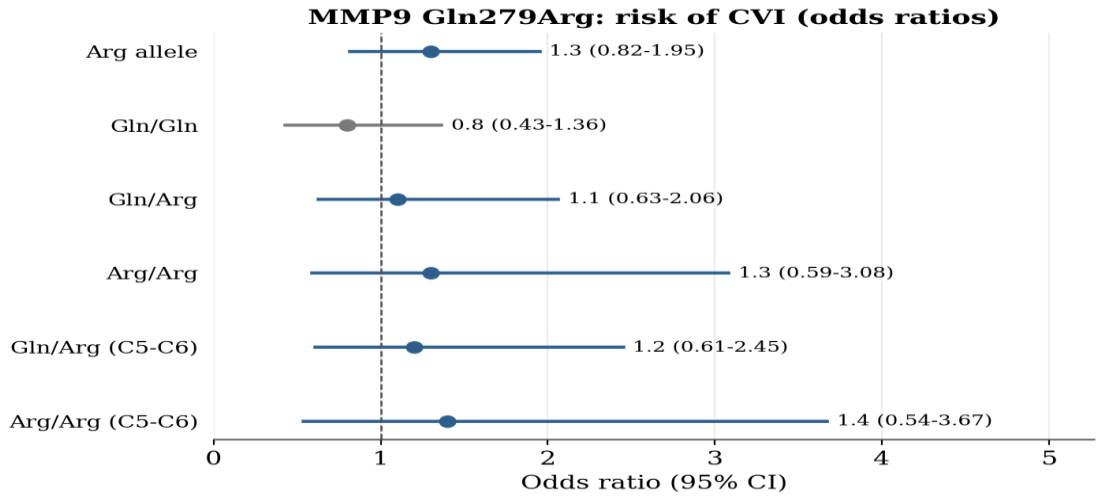

Figure 4. Odds ratios (with 95% confidence intervals) for the association of MMP9 Gln279Arg alleles and genotypes with CVI; the dashed line marks OR=1.

In the C5-C6 subgroup, the heterozygous Gln/Arg genotype reached OR=1.2 (95% CI 0.61-2.45) and the Arg/Arg genotype OR=1.4 (95% CI 0.54-3.67) relative to controls, indicating a moderate increase in the risk of severe forms among carriers of the unfavorable variants. By contrast, the Gln/Gln genotype displayed a protective tendency (OR=0.7; 95% CI 0.35-1.38). Thus the relative risk of CVI rose with detection of the heterozygous Gln/Arg genotype in C5-C6 patients and of the Arg/Arg genotype in both severity subgroups, consistent with aggravation of venous wall remodeling and progressive valvular incompetence.

4. Discussion

The clinical and instrumental data confirm a predominance of severe forms (CEAP C4-C6) in the studied cohort, with extensive trophic disturbances, oedema and combined patterns

of pathological reflux. These observations are consistent with the recognized burden of advanced CVD and with the central role of valvular incompetence and venous hypertension in disease progression [1, 2]. The almost universal presence of telangiectasia and oedema, together with a high frequency of healed and active venous ulcers, illustrates that a large share of patients reach medical attention only at advanced stages, when the spectrum of ultrasonographic abnormalities already exceeds the clinical picture. The observed tendency to hypercoagulation, more pronounced in C5-C6 patients, supports the concept of CVI as a prothrombotic, inflammatory state in which haemorheological disturbances accompany structural venous damage.

Matrix metalloproteinases are now regarded as key mediators of the degenerative process underlying venous insufficiency. The structure and function of the venous wall are partly regulated by different MMPs, which constitute a family of zinc-dependent metalloendopeptidases whose function is to cleave components of the ECM as well as non-matrix molecules such as receptors, growth factors, cytokines and chemokines - all of which are determinants of the tissue microenvironment [6]. MMP expression can be modulated by venous hydrostatic pressure, hypoxia and inflammatory reactions; moreover, MMPs may initiate remodeling of the venous wall through proteolytic cleavage of ECM components or by affecting the proliferation, programmed death and migration of medial smooth-muscle cells [3, 7]. MMP9 participates in the disorganization of denatured collagen and basement membrane, and a disequilibrium between MMP and TIMP activity in different segments of the varicose great saphenous vein wall supports its contribution to wall destabilization [12]. Histopathological studies likewise demonstrate altered MMP9 expression in varicose vein formation [13].

Our genetic results indicate that the unfavorable Arg allele and the Arg/Arg genotype of the Gln279Arg polymorphism contribute to the development of CVI, particularly its complicated C5-C6 forms, whereas the Gln/Gln genotype exerts a protective effect with respect to the prevention of severe forms. In both severity subgroups the relative risk increased with detection of the unfavorable genotypes, by approximately 1.2-1.4 times, which is patho-physiologically plausible given the role of MMP9 in ECM remodeling and progressive valvular incompetence. The principal cause of increased MMP9 activity in CVI is likely the imbalance between MMP and TIMP, leading to the accumulation of degraded ECM components in the wall of remodeled veins and thereby making MMP9 gene polymorphisms an important predisposing factor for disturbances of venous wall homeostasis.

These observations parallel reports linking elevated MMP9 with advanced CVD stages. A Polish study of MMP9 levels and growth factors in patients with CVD reported high MMP9 indices across CEAP classes C2-C5 [14], in agreement with the association of MMP9 with severe stages found here. A Slovak study analysing polymorphisms of MMP2, MMP8, MMP9 and TIMP2 reported that certain combined genotypes correlated with a higher risk of C4-C5 disease, although MMP9 alone could not be defined as an influential predictor in

that population [10]. By contrast, the study by Kunt and colleagues found no statistically significant difference for the MMP9 gene between patients with varicose veins and controls [9]. The divergence among these reports underscores the population-specific nature of MMP9 associations, which is governed by ethnic differences in allele and genotype frequencies and by gene-environment interactions.

From a translational perspective, the ability to detect a hereditary predisposition to CVI may contribute to early prognosis and to timely preventive intervention. More than 60% of patients with chronic venous disease have relatives affected by the same condition, and a substantial proportion of the patients in this study with detected mutations had first-degree relatives with CVI. Genetic counselling and pre-symptomatic DNA testing are therefore particularly relevant for individuals with a positive family history, allowing them to be informed of preventive measures and, where appropriate, referred to phlebologists or vascular surgeons. The principal limitation of this study is the modest sample size, which restricts statistical power for low-frequency genotypes and accounts for the wide confidence intervals; the absence of the rare Arg/Arg homozygote in some subgroup comparisons illustrates this constraint. Larger, multi-centre studies and combined multi-gene genotyping are required to define the relative contribution of MMP9 variants to venous pathology in this region, ideally complemented by measurement of circulating MMP9 to relate genotype to phenotype.

5. Conclusion

1. The clinical and ultrasonographic profile of the cohort was dominated by severe CVI (CEAP C4-C6) with extensive trophic changes and combined vertical and horizontal pathological refluxes, accompanied by a tendency to hypercoagulation that was more pronounced in C5-C6 patients.
2. The unfavorable Arg allele and the Arg/Arg genotype of the MMP9 Gln279Arg polymorphism showed a tendency towards association with CVI, increasing the risk of severe forms by approximately 1.3-1.4 times, while the Gln/Gln genotype displayed a protective effect.
3. Genotyping of the MMP9 Gln279Arg polymorphism, combined with clinical and instrumental assessment, may contribute to early, genetically informed prediction and prevention of CVI and its progression, and supports a personalized approach to patients with a positive family history.

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