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Frequency of Peripheral Arterial Disease in Patients With Chronic Venous Insufficiency

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Abstract

Background: It is estimated that about 15% (10% - 30% in most of the studies) of the total adult population has some aspects of the Chronic Venous Insufficiency (CVI). Frequency of the Peripheral Arterial Disease (PAD) in the adult population is 3% - 4%. Studies dealing with etiopathogenesis of leg ulcers show that between 10% and 18% of all ulcers are of mixed, arterial-venous origin.

Objectives: The purpose of this study was to find out if there is a higher frequency of PAD among CVI patients in comparison with the control group, as well as to discover some common risk factors for CVI and PAD.

Patients and Methods: This cross-sectional descriptive study was conducted at the dermatovenereological clinic, clinical center of Vojvodina, Serbia. A total of 162 examinees were included. All patients were examined for the existence of CVI and staged according to CEAP (Clinical, etiology, anatomy and patophysiology) classification. In this way, 3 groups were formed: Patients with the mild forms of CVI (stage 1 - 4 by CEAP classification), 57 patients; patients with the severe forms of CVI (stage 5 and 6 by CEAP classification), 55 patients; control group (no CVI), 50 patients. Also, the Ankle Brachial Pressure Index (ABPI) was assessed in all subjects, and its value of ≤ 0.9 was set as criteria for diagnosis of PAD. The same sample was divided according to the presence of PAD into two groups. The most important risk factors for CVI and PAD were identified for each patient through complete examination, medical record and appropriate questionnaire.

Results: Our results showed that the risk factors for CVI were high Body Mass Index (BMI), hypertension, predominantly standing position during work and positive family history for CVI. In the same sample it was found that 28 (17.28%) patients had PAD. Relevant risk factors for PAD in the present study were: high BMI, hypertension, diabetes and a positive family history for PAD. Comparison of frequency of PAD among patients with severe forms of CVI and control group showed that this difference was statistically significant (P = 0.0275; OR 3.375; 95% CI 1.125 - 10.12). After multivariate analyses, adjusted odds ratio OR was still statistically significant.

Conclusions: The peripheral arterial disease is more frequent in patients with the severe form of CVI, than in patients without CVI. Concomitant risk factors for CVI and PAD were high BMI and hypertension. In each patient with severe CVI it is necessary to determine the ABPI, in order to exclude the presence of PAD.

Keywords: Peripheral Vascular Disease, Venous Insufficiency, Risk Factors, Ankle Brachial Index, Leg Ulcer

1. Background

It is estimated that about 15% (10% - 30% in majority of studies) of the total adult population has some aspects of the Chronic Venous Insufficiency (CVI), with the significant increase among elderly people (1-4). Based on various epidemiological studies, it is estimated that the prevalence of lower limb ulceration in the adult population is about 1 - 2%. CVI acts as an etiological factor for the vast majority (70 - 90%) of these ulcers (5, 6).

Frequency of the Peripheral Arterial Disease (PAD) in the adult population is 3% - 4%. In older age the incidence of PAD is significantly increased (7, 8). It is estimated that the prevalence of PAD is three times higher when sensitive noninvasive tests for diagnostics of symptomatic and asymptomatic individuals are used (9, 10). It has been noted that the frequency of the mixed arterial-venous ulcers is between 10% and 18% (11-16).

Having all these data and assessments in mind, it is justified to assume that the frequency of PAD among individuals with CVI is higher compared to those without CVI.

2. Objectives

The aim of this study was to find out if there is a higher frequency of PAD among CVI patients in comparison with the control group, as well as to discover the most important common risk factors for CVI and PAD.

3. Patients and Methods

The cross-sectional descriptive study was conducted at the angiology department of the dermato-venereological clinic, clinical center of Vojvodina, Novi Sad, Serbia. This is a governmental institution, a university hospital and a tertiary referral center for whole province of Vojvodina (with approximately 2000000 inhabitants). Angiology department of the dermatovenereological clinic deals with patients with suspected venous pathology, and complete diagnostics and therapy is provided here.

Research was conducted in period 1st January 2009 - 31st December 2009. In this period, a total of 171 patients were examined for suspected CVI, but 9 of them were excluded from the study (unable to provide an informed consent (2), not having complete medical records (7)). After exclusion of those 9 subjects, a total of 162 examinees, all from region of Vojvodina, were included in the study, which corresponds with calculated sample size. We calculated sample size needed for this study using the Raosoft® (Raosoft, Inc.) sample size calculator. In this calculation, we accepted margin of error at the level of 5%, and power level of 80%.

Ethical approval for the research was obtained from both ethical comities of clinical center of Vojvodina and medical faculty in Novi Sad.

A study group was formed from patients who were referred to our department for suspected CVI, and in whom this diagnosis was confirmed after detailed examination, included Dupplex scanning of the lower extremities' veins. In every case of confirmed CVI, staging of venous disease according to the CEAP classification was determined. A control group was formed by patients who were also examined for suspected mild venous insufficiency, but, on the basis of clinical examination and dupplex scanning, did not have CVI.

The Ankle Brachial Pressure Index (ABPI) was determined in every patient included in the study–those with CVI as well as those without CVI. For the purposes of this study we used the CW Doppler device Smartdop 50EX, manufactured by Hadeco, Inc. The ABPI was determined as a ratio of the blood pressure of brachial artery and posterior tibial/dorsalis pedisartery (normal value range 0.9 - 1.1). Also, for every participant a questionnaire on the most important risk factors for CVI and PAD was filled out. Complete medical record about existence of diseases affecting peripheral vascular system, such as diabetes (fasting plasma glucose level $\geq$ 7.0 mmol/L), hypertension (systolic and diastolic blood pressure higher than 140/90 mmHg) and hyperlipidemia (total cholesterol > 6.2 mmol/L, triglycerides > 2.3 mmol/L) were investigated for every patient. These diseases were considered confirmed only if they were set by internist after appropriate laboratory testing. For every participant, determination of body weight and height, and arterial tension was carried out. In each case Body Mass Index (BMI) was calculated as an individual's body weight divided by the square of body height.

According to the presence of CVI and its CEAP (Clinical, etiology, anatomy and patophysiology) staging, all patients were divided into 3 groups:

1- Group 1: patients with mild forms of CVI (classes 1 - 4 by CEAP classification) - there were 57 patients included, 22 men and 35 women. Their mean age was 59.25 years (57.68 years for men and 60.23 for women).

2- Group 2: patients with severe forms of CVI (classes 5 and 6 by CEAP classification) - there were 55 patients included, 13 men and 42 women. Their mean age was 62.92 years (65.69 years for men and 62.04 for women).

3- Group 3: control group (no CVI), 50 patients were included, 19 men and 31 women. Their mean age was 59.65 years (57.95 years for men and 60.66 for women).

Peripheral Arterial Disease PAD was defined as ABPI value of $\leq$ 0.9. Same sample was divided according to the presence of PAD into two groups:

1- Group with PAD-28 patients with ABPI $\leq$ 0.9 were included.

2- Group without PAD-134 patients with ABPI > 0.9 were included (Table 1).

Statistical analyses were performed using SPSS 21 statistical program. Data about every risk factor for CVI were compared between the groups using the univariate statistical analysis for calculation of p value, as well as Odds Ratios (OR) with corresponding 95% confidence intervals. P values of < 0.05 were considered significant in all analysis. For estimation of difference between all three groups ANOVA was used. When two groups were compared (severe form of CVI vs. control group, severe form of CVI vs. mild form of CVI and control group), Fisher's exact test for categorical data and student t-test for quantitative data were used. For quantitative data, before using student t-test, normal distribution of data was tested using the Shapiro-Wilk test, as well as graphically presentation of data through Q-Q plot; those tests showed normal distribution of these data in our study sample. The univariate analysis (Fisher's exact test and student t-test for categorical and quantitative data, respectively) was also performed to calculate which risk factors showed a significantly higher frequency in the group with PAD compared to the group without PAD. The results of the analysis of risk factors for CVI as well as for PAD were used to create a statistical model for multivariate analysis, in order to calculate adjusted odds ratios as well as to estimate the correlation between CVI and PAD. For this purpose, logistic regression was used.

Table 1. Number of Patients With and Without Peripheral Arterial Disease in Each of the Three Chronic Venous Insufficiency Groups[a]

	With PAD	Without PAD	Total
Mild forms of CVI	8	49	57
Severe forms of CVI	15	40	55
Control group	5	45	50
Total	28	134	162

[a]Abbreviations: CVI, chronic venous insufficiency; PAD, peripheral arterial disease.

4. Results

By examining the existence of CVI, we found that 55 patients had severe forms of CVI, 57 mild forms of CVI, and in 50 we did not found the existence of CVI. The groups were homogeneous according to gender and age. An overview of the most important risk factors for CVI is presented in Table 2.

Using the methods of the univariate analysis, it was shown that group with severe forms of CVI had a significantly higher BMI compared with two other groups (30.66; 28.33; 26.05 kg/m^2) ($P < 0.0001$). Prevalence of hypertension was also significantly higher among patients with severe forms of CVI, comparing with other groups (69.09%/59.65%/46%) at level of significance $P < 0.05$. There were a higher proportion of patients with predominantly standing position during work among patients with severe forms of CVI, than in other two groups (75.93%; 64.91%; 52.94%) ($P < 0.05$). Family history of both varicose veins and venous ulcers was strongly associated with severe forms of CVI ($P < 0.0001$). Other risk factors, that we evaluated, were not significantly more frequent in any of the groups.

After dividing the same sample according to the presence of PAD, we formed two groups. The first group consisted of 28 patients with PAD, while the second group consisted of 134 patients without PAD. There is an overview of the most important risk factors for PAD in Table 3.

Table 2. Comparative Overview of the Most Important Risk Factors for Chronic Venous Insufficiency in all Three Groups[a]

	Severe forms of CVI (55)	Mild forms of CVI (57)	Control group (50)	P Values
Female gender[b]	76.36	61.4	62	0.207
Age, y	63	59.25	59,5	0.284
BMI, kg/m^2	30.66	28.33	26.05	< 0.0001
Diabetes[b]	10.91	8.77	10	0.858
Hypertension[b]	69.09	59.65	46	0.031
Hyperlipoproteinemia[b]	25.45	22.80	20	0.743
Smoking[b]	21.81	22.80	28	0.790
Work in a standing position[b]	75.93	64.91	52.94	0.048
Varicose veins in family[b]	89.09	70.18	30	< 0.0001
Venous ulcers in family[b]	38.18	14.04	2	< 0.0001
Woman who had deliveries[b]	92.86	88.57	90.32	0.835
Average number of deliveries	1.95	1.97	2.07	0.993
Spontaneous abortions[b]	30.95	31.43	19.35	0.449
Artificial abortions[b]	33.33	40	38.71	0.682
Contraception[b]	26.19	28.57	41.93	0.409

[a]Abbreviations: BMI, body mass index; CVI, chronic venous insufficiency.
[b]Values unit is (%).

Table 3. Comparative Overview of the Most Important Risk Factors for Peripheral Arterial Disease in PAD and No PAD Groups[a]

	PAD (ABPI < 0.9)	No PAD (ABPI > 0.9)	P Values
Female gender[b]	60.71	67.91	0.511
Age, y	64.29	59.79	0.068
BMI, kg/m^2	30.1	28.06	0.033
Diabetes[b]	21.43	7.46	0.036
Hypertension[b]	78.58	54.48	0.012
Hyperlipoproteinemia[b]	21.43	23.13	1.00
Smoking (present)[b]	21.43	24.67	0.812
Work in a standing position[b]	67.86	64.18	0.829
Arterial insufficiency in family[b]	14.29	3.73	0.049
Varicose veins in family[b]	57.14	65.67	0.395
Average number of deliveries	2.2	1.95	0.215
Spontaneous abortions[b]	29.41	27.47	1.0
Artificial abortions[b]	17.65	40.66	0.1
Contraception[b]	35.29	30.77	0.778

[a]Abbreviations: ABPI, ankle brachial pressure index; BMI, body mass index; PAD, peripheral arterial disease.
[b]Values unit is (%).

In group with PAD, average BMI was significantly higher than in group without PAD (30.1/28.06) ($P < 0.05$). Also, hypertension (78.58%/54.48%) and diabetes (21.43%/7.46%) were more frequent in the group with PAD (booth at level $P < 0.05$) comparing with group with no PAD. Family history for PAD was associated with presence of PAD ($P < 0.05$).

Taking the value of ABPI < 0.9 as a threshold for establishing the diagnosis of PAD, we found that total number of patients with PAD was 28 (17.28%) out of the total number of examinees (162). In the group with CVI there were 23 (20.53%) patients with PAD (15 in group with severe forms of CVI and 8 in the group with mild forms of CVI), while in the control group there were 5 (10%) patients with PAD. Comparing this data by univariate analysis (Fisher's exact test), there was no significant difference in frequency of PAD between patients with CVI of any degree and control group. However, when we compared frequency of PAD among patients with severe forms of CVI and control group, we found that this difference was statistically significant ($P = 0.0275$; OR 3.375; 95% CI 1.125 – 10.12). Similar results were obtained when we compared frequency of PAD among patients with severe forms of CVI with group of patients with mild forms of CVI and the control group ($P = 0.0267$; OR 2.712; 95% CI 1.182 – 6.218).

After adjusting for risk factors significant for severe forms of CVI (BMI, hypertension, type of job, and positive family history for varicose veins), by multivariate analysis we calculated adjusted odds ratios for the incidence of PAD in patients with severe CVI. We found out that PAD was still more frequent in the group with severe form of CVI comparing with group with mild forms of CVI and control group ($P = 0.038$; OR 3.109; 95% CI 1.062 – 9.103).

5. Discussion

By reviewing available literature, we found only a few papers about the association between varicose veins and arterial disease, and just one study that was specifically addressed to the incidence of PAD in patients with CVI.

All of these studies were population-based. In a study from 1981, Ducimetiere et al. found, after a follow up period of 6.5 years, that male employees aged 42 - 53 years with varicose veins had higher risk for intermittent claudication as well as for the coronary heart disease (17).

In Framingham study, authors found that men and women with varicose veins had a higher incidence of atherosclerotic cardiovascular disease than those without varicose veins, but only risk of coronary heart disease in women was statistically significant (18). A research based on the Normative Aging Study examined the association between varicose veins and symptomatic coronary heart disease. After 35 years of follow-up, the authors concluded that men with varicose veins were less likely to develop symptomatic coronary heart disease (19).

In the study of Makivaara et al. from Finland (2008) risk factors for artery disease (angina pectoris, myocardial infarction, PAD and cerebrovascular disease) were recorded in people with varicose veins. There was a 5-year follow-up period, with a total number of 6874 respondents. It was found that arterial disease occurred more frequently in patients with varicose veins (incidence OR of 2.0). Particularly PAD was associated with varicose veins, with incidence OR of 3.1. The authors concluded that varicose veins do not cause arterial disease but have common cause (20).

In the literature, a number of risk factors for the development of peripheral arterial disease and chronic venous insufficiency are described. For some of these risk factors there are very strong evidence, while for some it comes down to the domain of speculation. An overview of the most important risk factors for these diseases described in the literature is presented in the Box 1. The order in which the risk factors are listed in Box 1 is not necessarily linked to their importance in the etiopathogenic mechanisms of CVI and PAD (1, 6, 8, 20-24).

Box 1. Comparative Review of the Most Important Risk Factor Described in the Literature for PAD and CVI[a]

Risk Factors According to the Disease
Risk Factors for PAD
Older age
Gender: male
Obesity
Inheritance
Diabetes mellitus
Hypertension
Smoking
Elevated serum lipids
Physical inactivity
Hyperhomocysteinemia
Low kidney function
Risk Factors for CVI
Older age
Gender: female
Obesity
Inheritance
Occupation: standing position
Physical inactivity
Smoking
Number of deliveries and abortions
Contraceptives
Hypertension
Low intake of cellulose fibbers
Previous leg injuries

[a]Abbreviations: CVI, chronic venous insufficiency; PAD, peripheral arterial disease.

At this point, we must emphasize that this was not a population based study, but study on a specific sample of people who referred to our angiology department with suspected peripheral venous problem. All groups were homogenous by gender and age. It is well known that incidence of both diseases increases with older age, and is sex specific (male for PAD and female for CVI). We formed our control group to match study groups by age and gender in order to eliminate these well-known risk factors, and to try to find other common risk factors for these diseases. After analyzing our data, we found that common risk factors for CVI and PAD were increased BMI and hypertension.

In a number of studies, the association between obesity and diseases of veins was examined. In most of these studies such a connection was established, especially for women (17, 25). Data on such a relationship for men are much less consistent (9, 26). There are some studies in which this relationship was not established at all (27). Our results showed a relationship primarily between severe stages of CVI and increased BMI.

In our research, we used the CEAP classification for CVI staging. In most studies (especially not-so-resent ones) classification of CVI by stages was not performed at all, or it was not according to CEAP. These methodological differences may at least partly explain the differences in results between studies.

Is obesity itself a risk factor for the development of PAD, is not yet been clarified in the literature. It is the fact that with increasing body weight, other risk factors for PAD occur more often (hypertension, diabetes, dyslipidemia). The link between obesity and PAD is still quite unclear. In many studies no relationship between BMI and PAD was found (28-30). Other studies found a clear association (31, 32).

The connection of varicose veins and CVI with hypertension in the literature is not much processed. Evidences are uncertain if such a link exists. In two latest studies contradictory results were obtained. In study from Finland prevalence of varicose veins was higher in patients with PAD, and in patients with hypertension was not increased (33). In recent paper from UK, authors found that hypertension is significant risk factor for varicose veins, but they emphasizes that those results must be interpreted with caution because data of hypertension were based on history alone (34). In most epidemiological studies presence of hypertension was recorded based only by filling the questionnaire.

It is known that significant number of people have hypertension, without being aware of it. In our study, the presence of hypertension was confirmed with complete medical examination, including blood pressure measurement, and the majority of patients with hypertension also had a cardiologist report.

Hypertension has long been recognized as a risk factor for cerebrovascular and coronary heart disease. It leads to a more aggressive atherosclerosis in all segments of arterial circulation. In recent years, it has been recognized as a significant risk factor for the occurrence of PAD, with a similar mechanism of action in the peripheral arteries, primarily the femoro-popliteal segment (35).

Analysis of the data from the Framingham study showed that hypertension was a significant risk factor for virtually all of atherosclerotic cardiovascular disease, including PAD. It has been shown that the relative risk of PAD is 2 and 3.7 in males and females with hypertension, respectively (36).

As shown in this, as well as in some other previous studies, one can assume that PAD occurs more frequently in patients with CVI. Although our study sample is not very large, we believe that sufficiently indicates to this assumption, especially for severe forms of CVI. This finding has practical clinical significance in terms of extension basic diagnostic algorithm in patients with CVI, particularly those with severe forms, by determining of the ABPI. This is important, primarily because patients with the CVI and ABPI index below 0.9 require special caution when it comes to the application of compression therapy, in the sense that lower level of compression should be applied. In patients with CVI with ABPI values less than 0.5, application of the compression therapy is contraindicated (37). The existence of associated PAD in patients with CVI is often not so obvious, especially in those with most severe forms with large ulcers, when palpation of periphery pulses might be very difficult. Therefore, in the case of persistent ulceration, as well as of intolerance to compression therapy, one should take into account the possible existence of mixed arterial-venous etiology of peripheral vascular disease.

To discuss study limitations, population-based study (instead study on a specific sample) and larger sample size would better clarify the relationship between CVI and PAD. As this study was a cross-sectional one, it is not possible to estimate changes over the time.

Peripheral arterial disease is more frequent in patients with severe forms of chronic venous insufficiency comparing with the control group. Concomitant risk factors for CVI and PAD increased BMI and hypertension. The existence of concomitant risk factors could be a reason of increased frequency of PAD among CVI patients. In each patient with severe CVI, it is advisable to determine the ABPI, in order to exclude the presence of PAD.

Footnotes

Authors' Contribution: Milan Matic: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, study supervision, Aleksandra Matic: analysis and interpretation of data, statistical analysis, drafting of the manuscript, critical revision of the manuscript for important intellectual content, Verica Djuran: study supervision, administrative and technical support, Zorica Gajinov: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content,

Sonja Prcic: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, Zoran Golusin: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content.

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