

# Effects of diosmin-hesperidin and low pressure compression stocking combination in superficial venous insufficiency

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## Abstract

**Aim:** The main aim of the study is to investigate the efficacy and patient tolerance of Daflon 1000mg/day and low-pressure compression stocking combination in the treatment of superficial venous insufficiency.

**Materials and Methods:** This prospective study included 112 patients diagnosed with superficial venous insufficiency and reflux in saphenofemoral junction during March 2018 and 2019 at our center. All the patients received 1000 mg micronized purified flavonoid fractions containing 90% diosmin-10% hesperidin and low-pressure venous compression stockings (15-20 mmHg) throughout the study. Patients superficial, perforator, and deep venous systems were evaluated by Doppler US at the beginning and average of 5.3 ± 3.7 months after treatment.

**Results:** A total of 99 (88.4%) patients out of 112 eligible patients completed the investigation. The mean age was 41 ± 12.6, the female was 66 (58.9%), the mean follow-up was 5.3 ± 3.7 months. Pre-treatment and post-treatment diameters of SFJ were 6.27 ± 2.9 and 5.68 ± 1.8 mm, respectively, this was statistically significant (P=0.033). All of the patients have SFJ reflux initially, after the treatment, patients with SFJ reflux were decreased to 44 (44.4%), this was also statistically significant (P<0.001, OR:0.004, 95% CI: 0.0002-0.07). We also found significant improvement in grade III and grade IV reflux (P<0.05) after treatment. The symptomatic patients decreased from 63 to 16 after treatment, this was statistically severely significant (P<0.001, OR:0.11, 95% CI: 0.056-0.216). During the follow-up period, 6 (5.4%) patients were worsened and underwent surgical intervention, this was not statistically significant (P=0.076).

**Conclusion:** Daflon 1000mg/day with a combination of low- pressure CS well tolerates by venous insufficiency patients. Six months of continuous application may reduce the reflux of SFJ and VSM, and causes marked symptomatic relief.

**Keywords:** Chronic venous insufficiency; diosmin-hesperidin combination; edema

## INTRODUCTION

Chronic venous insufficiency (CVI) has been defined as clinical symptoms related to superficial, deep, or both venous system disruption of venous wall tone, valve dysfunction, and developing venous hypertension. It may develop congenitally or acquired. Pathology in the venous system can be either obstructive or non-obstructive (1). It can be seen in the adult age group 50% in European society. Also, there are studies showing chronic venous insufficiency in the 10-12 age groups (2). Treatment option of the superficial venous insufficiency includes stripping or ablation, whereas the compression and venotonic medication were the first line treatment of the deep venous insufficiency (3,4).

There is much evidence for inflammation that plays a role in the development of venous dysfunction and remodeling

of the venous valve from the first stage in CVI. Biochemical reactions arising from inflammation due to mechanical factors are responsible for the disruption of the venous system structure (5). The dilatation process of the venous structure is painful and may occur as heaviness in the leg, swelling, and paraesthesia (6). Skin changes may be seen as the earliest symptom of microcirculation dysfunction; however, edema is the most common clinical change (7). Serious edema table in different rates has been reported according to the degree of the CVI (8).

Food products have been widely used in Europe as vascular preservatives for many years. Micronized purified flavonoid fractions containing 90% diosmin and 10% hesperidin are considered as a potent therapeutic agent by cardiovascular surgeons to relieve symptoms caused by the CVI (9). Micronized purified flavonoid fractions containing 90% diosmin and 10% hesperidin

Received: 17.06.2020 Accepted: 06.08.2020 Available online: 26.01.2021

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affect microcirculation positively, normalizing the release of prostaglandins and free radicals. It reduces microvascular leakage caused by bradykinin; inhibits leukocyte activation, capture, and migration, also reduces venous hypertension (10).

On the other hand, compression stockings (CS) are an important tool in the treatment of varicose veins and venous insufficiency. They help to alleviate the symptoms of venous disease, prevent DVT and are used after varicose vein treatment. Now, CS is the mainstay of the non-pharmacological treatment of CVI. The pressure of CS differs from 10-50 mmHg, and the medium pressure (20-30 mmHg) is the most prescribed CS by the vascular physician. But difficulties in wearing and removing, rapid daily schedule, and patient intolerance are the main reason for the disuse of this armamentarium.

In this study, we aimed to investigate the efficacy and patient tolerance of Daflon 1000mg/day and low-pressure CS combination in the treatment of venous insufficiency by measuring SFJ valve competency and reflux.

## MATERIALS and METHODS

### Ethical disclosure

This study was carried out after approval of the Istanbul Medipol University Ethics Committee (number: 10840098-604.01.01-E.2696). Informed consent forms were signed by each participant. Hospital authority and all the authors accepted the study results and publication of the study.

### Study design

This prospective investigation was performed during March 2018 and 2019 at the Istanbul Medipol Mega University Hospital. All the patients were evaluated for lower extremity venous insufficiency by the independent radiologists at the first admission. The primary endpoint of the study was SFJ evaluation by Doppler US after minimal of six months of Daflon 1000mg/day and low-pressure CS treatment, the secondary endpoint was saphenous vein ablation or stripping due to advanced reflux and leg pain during the study period.

Patients who applied for an outpatient clinic for the first time were questioned in terms of symptoms and etiology of venous disease. In terms of venous insufficiency, deep, superficial, and perforating vein examination was done with Doppler US, SFJ diameter was measured and recorded in the predefined form. Eligible patients with superficial venous insufficiency were prescribed Daflon 1000mg and low pressure (15-21mmHg) compression stockings and were called for control 6 months later. After completing the treatment period, venous Doppler US was taken again and all venous structures were examined and the results were recorded. The pre-treatment and post-treatment results of the patients were loaded into the computer system and statistical analysis was performed. During the treatment period, patients who worsened in terms of venous insufficiency underwent venous ablation.

### Inclusion and exclusion

Patients newly diagnosed with venous insufficiency and have reflux in SFJ were included in the study. All the diagnoses were confirmed by the independent radiologists after evaluating the superficial, perforating, and deep venous systems.

Patients over the ages of 65 years, who had arterial pathology (ABI<0.80), had a history of deep vein thrombosis, and have active chronic venous ulcers were excluded. Patients who are not willing to wear CS were also not included.

### Statistical analysis

Statistical analysis was performed with the Statistical Product and Service Solutions (SPSS) software package (version 21.0, SPSS-IBM, Armonk, NY, USA). The normal distribution of the variables was examined by histogram graphs and the Kolmogorov-Smirnov test. Mean  $\pm$  standard deviation (SD) values were used to present descriptive analyzes. Pearson Chi-Square and Fishers Exact Tests were compared with 2x2 tables. While normally distributed (parametric) variables were evaluated among the groups, Student T-test was used. Mann Whitney U test was used to evaluate nonparametric variables. Logistic regression was performed to find the odds ratio. P-values below 0.05 were evaluated as statistically significant results.

## RESULTS

A total of 112 eligible patients were included initially, the mean age was 41 $\pm$ 12.6, the female was 66 (58.9%). During the study period, 5 patients underwent RF ablation, and one patient underwent stripping operation. Another 7 patients excluded from the study due to not wearing CS or discontinuation of Daflon. Thus, a total of 99 (88.4%) patients completed the investigation. The demographic characteristics of the participants were given in (Table 1).

Table 1. Patient characteristics

	N=112	%
Age (year)	41 $\pm$ 12.6	
Female	66	58.9
Male	46	41.1
Family history	28	25
Multiple child birth	14	12.5
Sedentary life	19	17.0
Obesity	23	20.5
Safeno-femoral junctional reflux	112	100
VSM reflux	85	75.9
Deep venous insufficiency	41	36.3
Mean follow-up (month)	5.3 $\pm$ 3.7	

The mean follow-up was 5.3 $\pm$ 3.7 months. Pre-treatment and post-treatment diameters of SFJ were 6.27 $\pm$ 2.9 and 5.68 $\pm$ 1.8 mm, respectively. The difference was statistically significant (P=0.033). All of the patients have SFJ reflux initially, after the treatment, patients with SFJ reflux were decreased to 44 (44.4%), this was statistically significant

( $P < 0.001$ , OR:0.004, 95% CI: 0.0002-0.07). When analyzing the reflux grade of VSM, we also found significant improvement in grade III and grade IV reflux ( $P < 0.05$ ). Patients with no reflux also increased significantly after treatment (17% vs. 32%,  $P = 0.015$ ). Daflon 1000mg and low-pressure CS combination were effective in treating junctional and VSM reflux.

The most frequent symptoms were leg pain and itching before treatment. The symptomatic patients decreased from 63 to 16 after treatment, this was statistically severely significant ( $P < 0.001$ , OR:0.11, 95% CI: 0.056-0.216). The combination treatment was found to be very effective in reducing symptoms of venous insufficiency (Table 2).

	Pre-treatment	Post-treatment	P value
SFJ diameter (mm)	6.27±2.9	5.68±1.8	0.033
Reflux at SFJ	99	44	<0.001
<b>Changes in the Grade of VSM reflux</b>			
Grade 0	17	32	0.015
Grade 1	18	21	0.592
Grade 2	21	17	0.471
Grade 3	43	22	0.002
Grade 4	17	7	0.035
Symptomatic patient	63	16	<0.001

During the follow-up period, 6 (5.4%) patients had increased symptoms and VSM reflux in spite of the regular treatment. But this worsening was not statistically significant ( $P = 0.076$ ). All of these patients were treated in success by surgical and RF ablation.

## DISCUSSION

The main findings of the study were that the Daflon 1000mg/day and low-pressure CS combination therapy was effective in treating SFJ and VSM reflux by reducing the SFJ valve diameter and supposedly structural recovery of the valve. These positive changes were also the main cause of symptomatic improvement.

SFJ valve pathologies play a role in the development of chronic venous insufficiency and symptoms becoming permanent (11). Depending on the increased venous pressure and disappearing venous tone, the diameter increases in the saphenofemoral junction and VSM. Irreversible damage may occur secondary to increased pressure and reflux in the deep venous system at the later stages of the disease (7). It was found that the micronized purified flavonoid fractions containing 90% diosmin and 10% hesperidin have a positive effect against failure in the saphenofemoral junction valves in rat experiments (12).

It is thought that disruption of the valve structure due to high pressure, presence of vascular obstruction, or severe oxygen radical damage plays a role in the basis of CVI (13).

An exact symptom may not be seen in the early stages of CVI; however pain, feeling of heaviness and rest in the leg, paresthesia, cramps that occur at night, and edema begin to appear when the process progresses. Often, we encounter with skin changes (14). Permanent edema, severe neurological receptor stimulation, and permanent symptoms begin to recur in a vicious circle due to the chronic inflammatory response seen after the development of fibrosis (15). In a study performed using micronized purified flavonoid fractions containing 90% diosmin and 10% hesperidin during the chronic inflammatory process, it was found that venous pressure was reduced (16). The feeling of heaviness in the leg, which is the most important finding of chronic venous pressure increase, decreased in all 106 patients included in our study. Pain, edema and itching are seen in all last stage CVI patients. Pain scales regressed after 6 months of treatment in our patients. The edema regressed in measurements and itching disappeared without any additional medical treatment.

## LIMITATIONS

This study included limited number of patients and revealed short-term results.

Only the outcomes before and after treatment were compared and the absence of a control group is an important shortcoming of our study. A large-scale randomized study and long term follow-up should be required.

## CONCLUSION

In conclusion, micronized purified flavonoid fractions containing 90% diosmin and 10% hesperidin with a combination of low-pressure CS well tolerates by the venous insufficiency patients. Six months of continuous application may reduce the reflux of SFJ and VSM, and marked symptomatic relief can also be expected.

*Conflict of interest : The authors declare that they have no competing interest.*

*Financial Disclosure: There are no financial supports.*

*Ethical approval: This study was carried out after approval of Istanbul Medipol University Ethics Committee (number: 10840098-604.01.01-E.2696).*

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