Preliminary comparative randomized blind study on effects of *Nexus-es*® elastic medical stockings in patients affected by chronic venous insufficiency of lower limbs

C. GRACI

Centro Sudi Flebologico Terme di Casciana
Casciana Terme, Pisa, Italy

Aim. **Chronic venous insufficiency represents a major health issue because of the high prevalence and the high direct and indirect costs. Compressive stockings are the mainstay of conservative approach, but in the daily clinical experience compliance is not optimal because of the lack of comfort. The objective of the study was to verify if a lower degree of compression obtained with stockings prepared with a special registered fiber *Nexus-es*®, enriched with extremely light, noble metals can reach the same results of stockings with a higher degree of compression.**

Methods. **Forty patients attending at the same specialistic center, with chronic venous insufficiency I, II have been randomized in two groups: the first group (20) used the 15 mmHg stockings *Nexus-es*® and the control group (20) used normal 25 mmHg stockings, indistinguishable for the patients.**

Results. **As expected, clinical signs (edema, superficial vein dilatation) and symptoms (heaviness), like parameters measured at light reflection rheography improved after six months of therapy in both groups. The improvement was similar in both groups; in the study group the same, positive result is achieved with a lower compression (15 mmHg instead of 25 mmHg). No adverse events have been reported in the course of the study.**

Conclusion. **The preliminary data shows a similar result in the study group achieved with a lower compression compared to the control group, probably through an improvement of tissue exchanges and oxygenation. In the daily clinical practice a lower compression drives to a better compliance and a better adherence.**

KEY WORDS: Venous insufficiency - Stockings - Electromagnetic fields.

The term chronic venous insufficiency describes a condition that affects the venous system of the lower extremities with venous hypertension, causing various signs and symptoms including dilated veins, heavy and tired legs, cramps, pain, swelling, edema, stasis dermatitis, hyperpigmentation of the skin, lipodermatosclerosis, and ulcerations.

Chronic venous insufficiency is a common problem that has a significant impact on afflicted individuals and on the healthcare system. Chronic venous insufficiency and its complications (that could drive up to lung embolism) are major health issues in developed countries. The considerable socioeconomic impact in Western countries is due to chronic venous insufficiency high prevalence, cost of investigations and treatment, loss of working days, disability payments and altered quality of life.

In Italy chronic venous insufficiency is the third disease, in terms of frequency, after allergies and hypertension: 19 million Italians are affected, 10-50% of the male population, over 50% of the female population. Only one out of three of them is aware of the disease and follows the correct therapy.[1]

Risk factors found to be associated with chronic venous insufficiency include age, sex (ordinarily, women make up the largest demographic), family history, obesity, pregnancy, phlebitis, and previous leg injury. There also may be environmental or behavioral factors associated with chronic venous insufficiency such as prolonged standing and perhaps a sitting posture at work.[2, 3]

The term chronic venous insufficiency represents the full spectrum of manifestations of chronic venous disease ranging from simple telangiectases or

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Corresponding author: C. Graci, via E. Toti 6, 56123 Pisa, Italy. E-mail: gracic@libero.it

reticular veins to more advanced stages, lesions of the skin and often of the subcutaneous tissues with the same pathogenetic mechanism: the chronic damage to the venous pumping function.[4] The dilated (varicose) superficial veins become progressively larger and more complex; varicose veins are prone to develop bouts of superficial thrombophlebitis. Edema that usually begins in the perimalleolar region, increases and ascends up the leg accumulating fluid. Edema presumably produces the pain by increasing intracompartmental and subcutaneous volume and pressure. There also may be tenderness along varicose veins from venous distention. The leg pain or discomfort is described as heaviness or aching after prolonged standing and relieved by elevation of the leg.

Obstruction of the deep venous system may lead to venous claudication, or intense leg cramping with ambulation. Cutaneous changes include skin hyperpigmentation from hemosiderin deposition and eczematous dermatitis. Fibrosis may develop in the dermis and subcutaneous tissue (lipodermatosclerosis). There is an increased risk of cellulitis, leg ulceration, and delayed wound healing. Long-standing chronic venous insufficiency also may lead to the development of lymphedema, representing a combined disease process.

The manifestations of chronic venous insufficiency have been classified in a clinical scheme: the CEAP (Clinical, Etiology, Anatomic, Pathophysiology classification) developed by an international consensus conference.[5] Because many of CEAP components, which is the worldwide standard for describing the clinical features of chronic venous disease, are relatively static, a disease severity scoring scheme with gradable elements, that can change in response to treatment, was developed in 2000 by the American Venous Forum.[6] The venous severity scoring system (VESS) is based on different scores:

the first is a Venous Clinical Severity Score (clinical characteristics of chronic venous disease graded from absent to severe);

the second is a Venous Anatomic Segmental Disease Score, entirely based on venous imaging which combines the Anatomic and Pathophysiologic components of CEAP assigning a numerical value to segments of the venous system in the lower extremity;

a third score, the disability score is a modification of the existing CEAP disability score and comes from the ability to perform normal activities of daily living with or without compressive stockings.

The venous severity scoring has been shown to be useful as an evaluative instrument to assess changes in disease severity over time and in response to treatment.[7]

Based on initial experiences with the VCSS, an international ad hoc working group of the American Venous Forum has updated the instrument clarifying ambiguities, updating terminology, and simplifying application.[8]

In the diagnosis of chronic venous insufficiency there are important non-invasive techniques: venous Duplex imaging and photoplethysmography (PPG) or light reflection rheography.[9, 10] The latter studies blood flow and blood volume changes in the skin through a light source and a light-sensitive diode that detects changes in the number of red blood cells in the dermis.[11] Red blood cells absorb maximum light in the sitting or standing position when the pressure is high and the veins are full. Venous plexuses become less full and light absorption decreases as the venous pressure falls with exercise.

Regarding the treatment of chronic venous insufficiency, the practitioner should be able to recognize the manifestations of chronic venous insufficiency and use confirmatory testing. Specific treatment is based on severity of disease, patients with uncorrected advanced chronic venous insufficiency are at risk for ulceration, recurrent ulceration, and nonhealing venous ulcers with progressive infection and lymphedema.

The initial treatment of chronic venous insufficiency involves conservative measures to reduce symptoms and prevent the development of secondary complications and the progression of disease. The use of compressive stockings is the mainstay of conservative treatment. The use of graded elastic compressive stockings (with 20 to 50 mmHg of tension) is well established in the treatment of chronic venous insufficiency and compression stockings have been shown to reduce reflux in vein segments.[12]

If conservative measures fail or provide an unsatisfactory response, then further treatment should be considered based on anatomic and pathophysiological features. CEAP clinical classes 4 to 6 often require invasive treatment.

As chronic venous insufficiency has been known since ancient times, bandages since Neolithic [13] and Hippocrates used bandaging to treat chronic venous insufficiency. A preliminary therapeutic considera-

tion for all CEAP clinical classes of chronic venous insufficiency is compression therapy to provide graded external compression to the leg and oppose the hydrostatic forces of venous hypertension.[14] Several studies have investigated the hemodynamic benefits of compression therapy in patients with chronic venous insufficiency. Adequate compression produces through a greater tissutal pressure the decrease of venous caliber, a best closure of valvular flaps and eventually reduction of pathological refluxes up to 30-40%.[15] Both the blood volume in the lower limbs and venous capacity decrease, while the right ventricular filling and blood rate increase. Treatment with 30 to 40 mmHg compression stockings results in significant improvement in pain, swelling, skin pigmentation, activity, and well-being if compliance of 70% to 80% is achieved.[16] With a structured regimen of compression therapy 93% of patients with venous ulcers can achieve complete healing at a mean of 5.3 months.[17]

Elastic compression stockings in chronic venous insufficiency has to take in account two factors: tension and length. The tension is based on the clinical severity:[18]

— 20 to 30 mmHg for CEAP classes 2 to 3;
— 30 to 40 mmHg for CEAP classes 4 to 6;
— 40 to 50 mmHg for recurrent ulcers.

The length of the compressive stockings is inversely proportional to patient compliance; with knee-length stockings patient adherence is greater, the use of thigh- or waist-high stockings may be necessary in patients with edema extending above the knee, but these stockings are more difficult to use.

Tolerability and difficult in wearing the compressive stockings are limiting factors in chronic venous insufficiency therapy, as confirmed by a recent study: in 70% of the cases prescription has not been followed because of lack of comfort.[12]

The research has developed in the Eighties particular textile fibers where noble metals are fused to polyester at high temperature. *Nexus-es*® is a special, patented fiber, containing in its inner mixture Platinum, Titanium and Aluminium molecules. Platinum, Titanium and Aluminium are very light, ductile, resistant and highly conductive metals; in these metals following an increase of temperature (sun radiation, body temperature) excited electrons pass from low energy to high energy stages. The length of the micro metal filaments determines the frequency of vibration and the wavelength comprised for *Nexus-es*® between 4 and 14 µm. Due to its microfilaments *Nexus-es*® shows particolar electrophysical properties as infrared emission and vibrational/rotational excitation of water particles. It has been demonstrated that if submitted to an electromagnetic radiation of the same wavelength of water molecules, the negative charge of water particle is attracted to one side and the positive charge towards the other side; therefore the whole water particle starts to rotate.[19] Usually water particles because of their shape and electric charge are linked each other in big reticules, named clusters, composed by a hundred of water particles.[20] At bodily temperature nearby 40% of water is organized in clusters, with the solutes trapped inside the clusters. When the water particles start to rotate, water clusters are broken, and the solutes, the nutritive substances, the catabolits are released [21] (Figure 1).

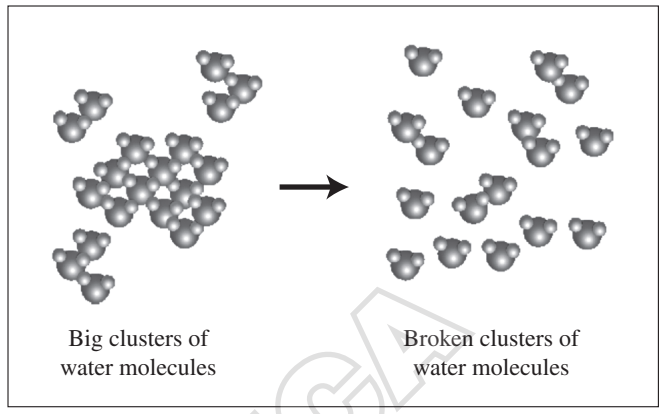

Figure 1.—Water clusters.

On this basis for the *Nexus-es*® fiber has been assumed an active effect on the microcirculation and on exchanges between tissues and vessels, with an improvement of vein function, and clinical and hemodynamic parameters.

The hypothesis of this study is that the effect of *Nexus-es*® allows a lower degree of compression than the usual compressive stockings, with a strong improvement of tolerability and compliance.

Materials and methods

The study enrolled 40 subjects with chronic venous insufficiency I-II, all attending the "Centro Studi Flebologico delle Terme di Casciana" in 2008. The subjects signed the informed consent. Patients

TABLE I.—*Demographic characteristics of the two groups.*

	Study group (N.=20)	Control group (N.=20)
Sex		
Males	2	2
Females	18	18
Age		
Mean	35	35
SD	14	15

TABLE II.—*Clinical examination at baseline.*

	Study group (N.=20)	Control group (N.=20)
Edema	++	++
Dilated superficial veins	+++	+++
Heaviness	+++	+++

were men and women, aged 18-65 years, without relevant concomitant pathologies and without signs of arterial disease. All subjects worked in prolonged standing position (barman, shop assistant) and denied smoking habit.

The study was conducted in accordance with local laws and ethical requirements. Patients were randomized in two groups: 20 in the study group, wear the compressive stocking *Nexus-es*® available in three sizes (M, L, XL) with degree of compression 15 mmHg; 20 patients, in the control group, used common compressive stockings (25 mmHg).

Patients were prescribed to wear the stockings for the whole day, and were not aware which kind of stockings they were wearing. The study has lasted for six months.

The objective of the study was to demonstrate that the fiber 15mmHg *Nexus-es*® produces the same results of a "normal" 25mmHg stocking, with a better tolerability and compliance for the patient.

The outcomes were the following:

• clinical parameters:

— symptoms as heaviness;

— signs assessed by the physician as edema and dilated superficial veins;

• instrumental assessments:

— light reflection rheography;

— ecocolor-Doppler.

Patients were visited and performed clinical and instrumental evaluation at T0 and after six months of therapy. All assessments have been performed by the same physician for all patients and at both visits.

TABLE III.—*Light reflection rheography examination at baseline.*

	Study group (N.=20)	Control group (N.=20)
T (s)	25.7±9.3	25.2±9.7
Delta R (mV)	245.4±72.7	240.5±80.1

Results

Forty patients were enrolled in the study and randomized. All enrolled patients followed the protocol and ended the study according to prescription.

All patients have been analyzed; no protocol deviations have been reported.

Demographic characteristics of the two groups are reported in Table I; the two groups were homogeneous for sex, age and working activity. In both groups there were 18 females, while male subjects were only two; the mean age was 35±15 in the study group (*Nexus-es*® 15 mmHg stockings) and 35±14 in the control group ("normal" 25 mmHg stockings).

At baseline clinical and instrumental parameters have been recorded and are reported in Tables II, III. Signs and symptoms severity are exactly alike at baseline in the study group and in the control group. The difference in light reflection rheography measures between the two groups are not significant; the color ultrasonography exam shows the same results in both groups.

After six months of treatment patients were visited for the second time. The physician asked the patients if they have followed the prescription within the last six months. All patients confirmed they have followed the therapy.

In both groups after six months clinical signs and symptoms (edema, dilated superficial veins, heaviness) show an improvement as described in Figure 2. Light reflection rheography parameters improve similarly in both groups (Table IV and Figure 3) without statistical significant difference ($P<0.05$) detected between the two groups. The color ultrasonography does not show any relevant difference.

No adverse events were reported in the course of the study.

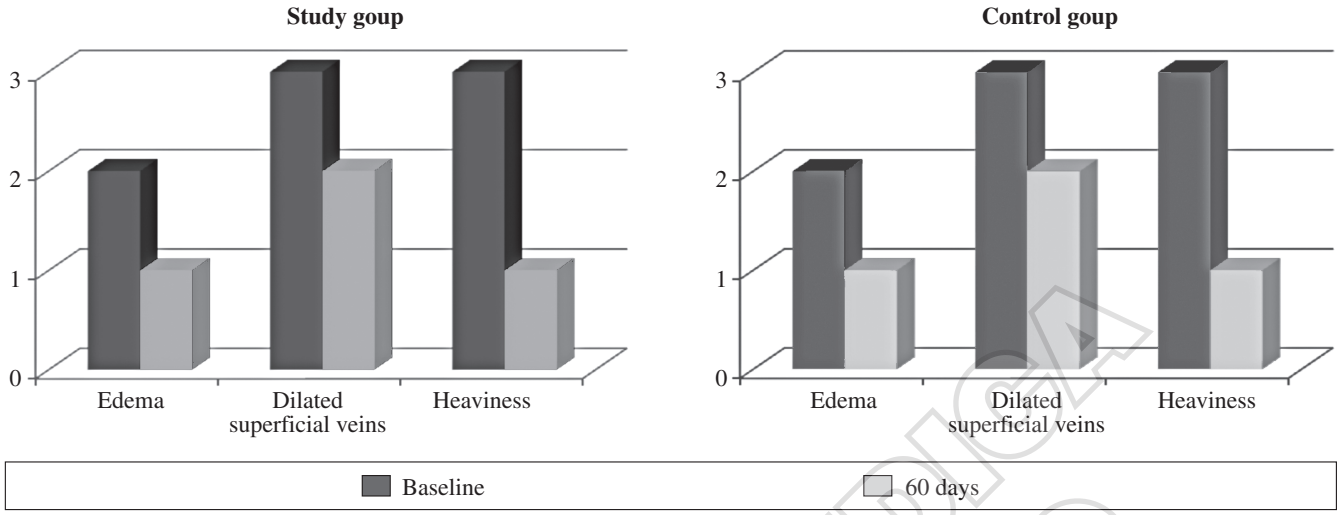

Figure 2.—Signs and symptoms decrease after 60 days of treatment.

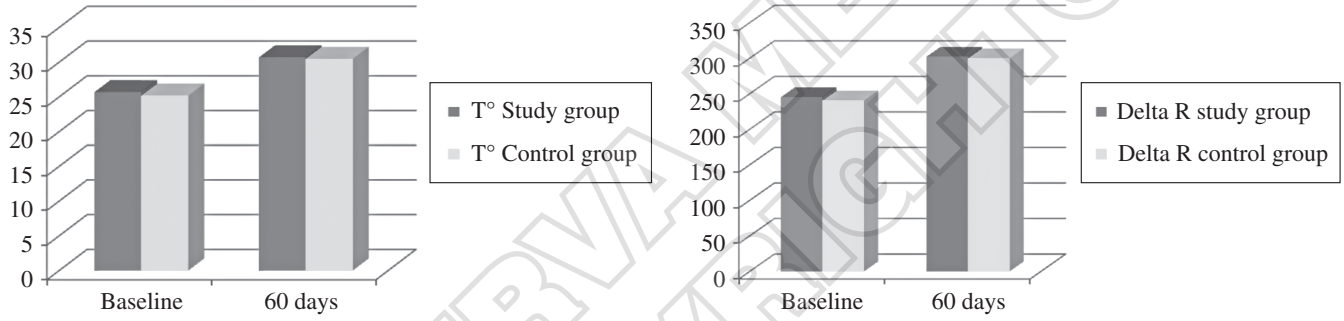

Figure 3.—Rheographic parameters at baseline and after 60 days of treatment.

TABLE IV.—*Light reflection rheography examination at baseline and at day 60.*

	Study group (N.=20)		Control group (N.=20)	
	Baseline	60 days	Baseline	60 days
T (s)	25.7±9.3	30.7+3.9	25.2±9.7	30.5+4
Delta R (mV)	245.4±72.7	302.3+31.3	240.5±80.1	300+25.5

Discussion

As expected, in patients with chronic venous insufficiency I-II compressive stockings represent an important and useful therapy. The results show the same results in terms of efficacy both in the study group (patients wearing 15 mmHg *Nexus-es*® stockings) and in the control group (patients wearing "normal" 25 mmHg stockings). Both stockings improve the symptoms reported by the patients (heaviness), the signs observed by the physicians (edema and dilated superficial vein), and the results recorded during the light reflection rheography. The entity of the improvement is equivalent in both groups. It is very interesting that the same results have been obtained in the study group, with a lower compression (15 mmHg), and in the control group (higher compression, 25 mmHg).

The opportunity to obtain a significant improvement with a lower degree of compression, and there-

fore with a more acceptable treatment, may represent in the daily clinical practice the opportunity of a best compliance and adherence to treatment. In fact, as widely reported in the literature, the main limiting factor for a correct use of compressive stockings is tolerability of compression.

The factor that allows to fill the gap between the lower (15 mmHg) and the higher (25 mmHg) compression can be ascribed to the properties of the enriched fiber *Nexus-es®*.

The fiber emits infrared between 4 and 14 μm, with an anti-clusters effect; eventually the *Nexus-es®* fiber makes easier metabolic exchanges at tissue levels, improves the oxygenation and the removal of inflammation mediators and substances stimulating nociceptors. The fast reduction of edema can be possibly due to the improvement of the rate of exchanges between vessels and tissue.

Conclusions

Data collected in this study are preliminary and need to be confirmed by the analysis of a wider sample. The important aspect of results obtained by the new enriched *Nexus-es®* fiber with a lower compression compared to the "normal" compressive stockings has to be investigated in depth; in particular the tolerability and the compliance to therapy should be carefully measured with specific questionnaires for patients. Nevertheless, the data collected in this study represent, in our opinion, a significant evidence in the field of the compressive therapy of chronic venous insufficiency, a major and increasing health issue.

Riassunto

Studio comparativo preliminare sull'effetto delle calze compressive Nexus-es® nell'insufficienza venosa cronica degli arti inferiori

Obiettivo. L'insufficienza venosa cronica rappresenta un importante problema sanitario a causa della sua notevole prevalenza e dei suoi elevati costi diretti e indiretti. Le calze compressive rappresentano un cardine dell'approccio conservativo all'insufficienza venosa cronica, ma nella pratica clinica quotidiana l'aderenza al trattamento non è ottimale a causa della scomodità. L'obiettivo dello studio è verificare se un livello di compressione inferiore, ottenuto con calze preparate con una speciale fibra tessile brevettata che contiene molecole di metalli nobili, leggeri, Nexus-es®, possa ottenere gli stessi risultati di una calza a più elevato grado di compressione.

Metodi. Quaranta pazienti con insufficienza venosa cronica I, II afferenti allo stesso centro flebologico, sono stati randomizzati in due gruppi omogenei: 20 hanno utilizzato una calza compressiva Nexus-es® 15 mmHg e 20 una calza in normale tessuto elastico 25 mmHg, indistinguibile per i pazienti.

Risultati. Come atteso, dopo sei mesi di trattamento sono stati dimostrati miglioramenti in entrambi i gruppi; sia nei segni clinici come edema e dilatazione del circolo venoso superficiale, che a livello sintomatologico (senso di pesantezza), e nei parametri misurati alla reografia a luce riflessa. Il miglioramento era sovrapponibile nei due gruppi; ma nel gruppo di studio il risultato positivo è stato ottenuto con un livello di compressione inferiore (15 mmHg invece di 25 mmHg). Nel corso dello studio non sono stati registrati né riferiti eventi avversi.

Conclusioni. I dati preliminari raccolti in questo studio mostrano un risultato sovrapponibile ottenuto nel gruppo di studio con un livello di compressione inferiore rispetto al gruppo di controllo, probabilmente attraverso un miglioramento degli scambi tessutali e dell'ossigenazione. Nella pratica clinica quotidiana tutto questo si traduce in una compliance migliore e quindi una migliore aderenza alla terapia.

PAROLE CHIAVE: Insufficienza venosa - Calze compressive - Campi elettromagnetici.

References

1. Calzolari G. L'insufficienza venosa cronica terza patologia più diffusa in Italia. SM-Stampa medica. 20 maggio 2007. [accessed 2001 January 23; cited 2011 March 2]. Available at: http://www.stampamedica.it/medicina/news/738-linsufficienza-venosa-cronica-terza-patologia-piu-diffusa-in-italia.html Ultimo
2. Jawien A. The influence of environmental factors in chronic venous insufficiency. Angiology 2003;54:S19-S31.
3. Lacroix P, Aboyans V, Preux PM, Houles MB, Laskar M. Epidemiology of venous insufficiency in an occupational population. Int Angiol 2003;27:172–6.
4. Weingarten MS. State-of-the-Art treatment of chronic venous disease. Clinical Infectious Diseases 2001;32:949–54.
5. Nicolaides AN; Members of the Executive Committee. Classification and grading of chronic venous disease in the lower limbs: a consensus statement. In: Gloviczld P, Yao IST, editors. Handbook of venous disorders. London: Chapmanand Hall; 1996. p. 652-60.
6. Rutherford RB, Padberg FT, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. J Vasc Surg 2000;31:1307-12.
7. Kakkos SK, Rivera MA, Matsagas MI, Lazarides MK, Robless P, Belcaro G et al. Validation of the new venous severity scoring system in varicose vein surgery. J Vasc Surg 2003;38:224-8.
8. Vasquez MA, Rabe E, McLafferty RB, Shortell CK, Marston WA, Gillespie D et al. american venous forum ad hoc outcomes working group. Revision of the venous clinical severity score: venous

outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg 2010;52:1387-96.
9. Stemmer R, Marescaux J, Furderer CR. Photo-reflex rheography and diagnosis of deep venous thrombosis. Phlebologie 1984;37:69-75.
10. Furderer CR, Stemmer R, Marescaux J. Non-invasive functional exploration using photo reflexometry. Phlebologie 1984;37:417-24.
11. Nicolaides AN, Miles C. Photoplethysmography in the assessment of venous insufficiency. J Vasc Surg 1987;5:405–12.
12. Zajkowski PJ, Proctor MC, Wakefield TW, Bloom J, Blessing B, Greenfield LJ. Compression stockings and venous function. Arch Surg 2002;137:1064-8.
13. The Compression Therapy Study Group Consensus Conference on Compression Therapy [Internet]. [cited 2011 March 2] Available at: http://www.terapiacompressiva.it/
14. Leskovec NK, Pavlovic MD, Lunder T. A short review of diagnosis and compression therapy of chronic venous insufficiency. Acta Dermatoven APA 2008;1:17-21.
15. Mariani F, Mancini S, Volterrani L. La compressione degli arti inferiori con tutore elastico: studio morfologico dei vasi periferici con T.A.C. Atti del III Congresso Internazionale di Flebolinfologia, Ferrara-S. Marino 18-21 settembre 1991;4.24-4.26
16. Motykie GD, Caprini JA, Arcelus JI, Reyna JJ, Overom E, Mokhtee D. Evaluation of therapeutic compression stockings in the treatment of chronic venous insufficiency. Dermatol Surg 1999;25:116–20.
17. Mayberry JC, Moneta GL, Taylor LM, Porter JM. Fifteen-year results of ambulatory compression therapy for chronic venous ulcers. Surgery 1991;109:575–81.
18. Eberhardt R, Raffetto JD. Chronic venous insufficiency. Circulation 2005;111;2398-409.
19. Keutsch FN, Saykally RJ Water clusters: Untangling the mysteries of the liquid, one molecule at a time. PNAS 2001;98:10533-40.
20. Clegg JS. Intracellular water, metabolism and cell architecture: part 2. In: Fröhlich H, Kremer F, editors. Coherent excitations in biological systems, editor. New York, NY: Springer-Verlag; 1983. p. 162-77.
21. Del Giudice E, Preparata G, Fleischmann M. QED coherence and electrolyte solutions. J Electroanal Chem 2000;482:110-6.