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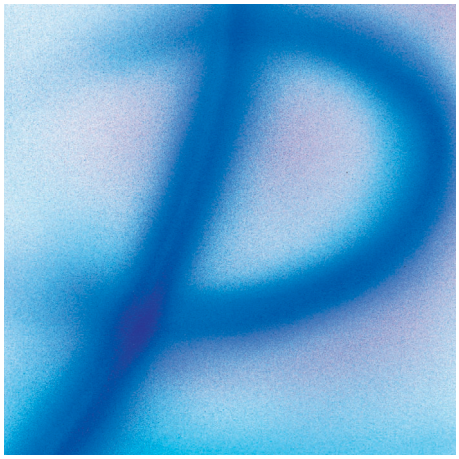

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AIMS AND SCOPE

Phlebolymphology is an international scientific journal entirely devoted to venous disease.

The aim of *Phlebolymphology* is to provide doctors with updated and interesting information on phlebology and lymphology written by well-known specialists from different countries worldwide.

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, was included in the EMBASE database in 1998.

Phlebolymphology is made up of several sections: editorial, articles on phlebology and lymphology, news, review, and congress calendar.

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CONTENTS

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PHLEBOLYMPHOLOGY

The articles in this issue of Phlebolymphology *deal with very interesting areas of phlebolymphology.*

A special mention is to be given to the Latin American consensus on the management of lymphedema which held its prior conference under the chairmanship of Dr Ciucci. We do welcome this excellent initiative.

New proposals for a classification of primary varicose veins of the lower extremities have come from a Latin American consensus group under the leadership of ***Roberto Simkin*** *and* ***Jorge Ulloa****. The authors state that their intention is not to replace the CEAP classification, but to simplify and to refine the clinical segment of the "C." This initiative contributes to the ongoing discussion on making the CEAP more user-friendly.*

During recent years basic research has provided fascinating new insights into the pathophysiology of venous ulceration. ***Dr Herouy*** *from the Dermatological University clinic in Freiburg, Germany, gives a stimulating review on the role of matrix metalloproteinases and their inhibitors in venous leg ulcer healing.*

Many years ago, van der Molen had already proposed the term "chronic venolymphatic insufficiency" as being more appropriate than the commonly used "chronic venous insufficiency" (CVI). However, up to now the role of the lymphatic drainage in any form of CVI is still highly neglected. ***Pearson and Mortimer*** *present a convincing survey on the close relationship between venous and lymphatic anatomy and pathophysiology. The main targets of any kind of treatment in patients with CVI are:*

1. *A decrease in capillary filtration, and*
2. *An improvement in lymphatic function.*

Encouraging data show that these two effects may also be obtained by medications containing micronized purified flavonoid fraction (MPFF), so such drugs may offer a useful adjunctive treatment modality.

Prof Dr Hugo Partsch

The role of matrix metalloproteinases (MMPs) and their inhibitors in venous leg ulcer healing

Yared HEROUY

From the Department of Dermatology, University Hospital, Freiburg, Germany

SUMMARY

Different hypotheses have been postulated to describe the cause of venous leg ulceration including the "fibrin cuff hypothesis" with pressure-damaged capillary vessels and the "white cell trapping hypothesis" based on accumulated leukocytes. To date, several studies have revealed the important role of matrix metalloproteinases (MMPs) in the process of venous leg ulcer formation and contributed significantly to better understanding of the pathogenesis of venous leg ulcers. MMPs, also known as matrixins, hydrolyze components of the extracellular matrix. Currently over 20 MMP genes have been identified in humans, and most are multidomain proteins. These enzymes had been shown to generate an epidermal and dermal skin defect in lipodermatosclerosis, the stage preceding venous leg ulcers. In addition, misregulation of MMP activity and TIMP-mediated counterregulation in the wound fluid and wound bed contribute to impaired and prolonged wound healing of venous leg ulcers. However, there is also accumulating evidence indicating that several distinct matrixins are also repair-associated and not only prolonging factors. Therefore, the role of matrixins during leg ulcer healing has to be regarded in a differentiated way, and has to consider spatial and temporal factors. This review describes different members of the matrixin family and discusses substrate specificity, domain structure and function, the activation of proMMPs, the regulation of matrixin activity by tissue inhibitors of metalloproteinases (TIMPs), and their pathophysiological implication in severe stages of chronic venous insufficiency.

INTRODUCTION

Proteolytic degradation of the extracellular matrix (ECM) is an important process during venous ulcer formation and healing. Several investigations have provided evidence that matrix metalloproteinases (MMPs), collectively called matrixins, participate strongly in different stages of the ulcerative process, from their formation with the initial epithelial defect until ulcer resolution and repair. The ECM is important for creating the cellular environments required during morphogenesis. MMPs are proteinases that participate in ECM degradation.[1,2]

Keywords:
Proteinases, metalloproteinase, chronic venous insufficiency, lipodermatosclerosis, varicose veins, venous leg ulcers

Under physiological conditions, the activities of MMPs are precisely regulated at the level of transcription, activation of the precursor zymogens, interaction with specific ECM components, and inhibition by endogenous inhibitors.[1,2] It was postulated that a loss of activity control may result in different diseases such as arthritis, atherosclerosis, nephritis, aneurysms, fibrosis, and cancer.[3] Specific inhibitors of matrixins are tissue inhibitors of metalloproteinases (TIMPs) that participate in controlling the local activities of MMPs.[4,5] The pathological effects of MMPs in chronic venous insufficiency that involve vascular remodeling, and skin tissue instability, as well as inflammatory processes, are of major interest. In the following review, we give an overview of the structure, function, and biochemistry of MMPs and their inhibitors, and provide insight into the pathogenic role of MMPs in lipodermatosclerosis, during the wound healing process of venous leg ulcers, and into modalities to influence their proteolytic properties.

Causes of venous leg ulcers – different hypotheses

Chronic venous insufficiency is associated with venous hypertension, leading, in complicated cases, to venous leg ulceration. The main histological features of advanced stages of chronic venous insufficiency such as lipodermatosclerosis are loss of papillary structures in the dermal-epidermal junction zone, dermal pericapillary fibrin cuffs, and fibrosis of the reticular dermis, whereas venous ulcers are characterized by total loss of epidermal and partly dermal cellular and matrix tissue components.[6] In the "fibrin cuff hypothesis", pressure-damaged capillary vessels are made responsible for leakage of fibrinogen.[7] In contrast, the "white cell trapping hypothesis" is based on the presence of toxic metabolites and proteolytic enzymes caused by accumulated leukocytes damaging capillary vessels.[8] Finally, cytokines released by leukocytes have been suggested to stimulate endothelial cells and fibroblasts to synthesize pericapillary fibrin cuff-forming molecules.[6] Impairment of gas and nutrient exchange between plasma and dermis had been suggested as common features, resulting in ulcer formation. Although different hypotheses had suggested underlying factors in the pathophysiology of ulcer formation, there had been great controversy as to how increased tissue pressure may result in such drastic cellular and matrix changes of venous ulcerations. Pericapillary fibrin cuffs are complex structures containing whorls of molecules such as laminin, fibronectin, tenascin, and type I and III collagens.[9] They may be synthesized in response to increased venous pressure to protect the vessels and enable them to withstand the higher pressures. Such cuffs may inhibit capillary sprouting, so limiting angiogenesis and neovascularization, as well as acting as a barrier to gases and nutrients. Degradation of the cuffs by proteases may release endothelial cells and pericytes from adhesive environments and so facilitates sprouting and angiogenesis, as well as improving tissue nutrition and oxygenation, thereby supporting wound healing of venous ulcers. However, these alterations depend on the dynamics of matrix turnover, due to proteolytic properties of specific matrix-degrading endopeptidases in advanced stages of venous insufficiency.

Extracellular matrix and its turnover

The ECM is often viewed as the "scaffolding" that supports the cellular components of various tissues. It is now recognized that in addition to their structural functions, the components of the ECM serve as modulators of cell growth and tissue differentiation. The latter results in changing dynamics between the cellular and stromal matrix elements. Changes in matrix composition require the removal of the previous extracellular components. This is accomplished through the action of proteases, which selectively degrade matrix macromolecules and may alter cell-matrix attachments.[10] Matrix removal and synthesis occur simultaneously in an orderly and progressive fashion. The end stage of differentiation is a homeostasis achieved between new matrix formation and matrix turnover. Turnover of the ECM is a unique biological problem because of the high collagen content of most ECM structures and the resistance of these triple helical macromolecules to cleavage of most proteases. It is well recognized that connective tissue remodeling, either physiological or pathological, is in most cases a highly organized process that involves the selective action of MMPs, that collectively degrade major components of the ECM.[11]

The family of matrix metalloproteinases

MMPs play an important role in the remodeling of the ECM. Recent studies have increased the list of biological processes in which MMPs appear to be involved, and in several cases pointed to processes that do directly involve matrix remodeling. These enzymes constitute a family of several zinc-dependent endopeptidases which are expressed at low levels in normal adult tissues. They are upregulated during different normal and pathological

remodeling processes such as embryonic development, tissue repair, inflammation, tumor invasion, and metastasis.[12-14] MMPs are known to be proteases that can cleave collagen macromolecules, which are of significant importance in maintaining the architecture and integrity of skin. MMPs belong to a growing family of soluble and

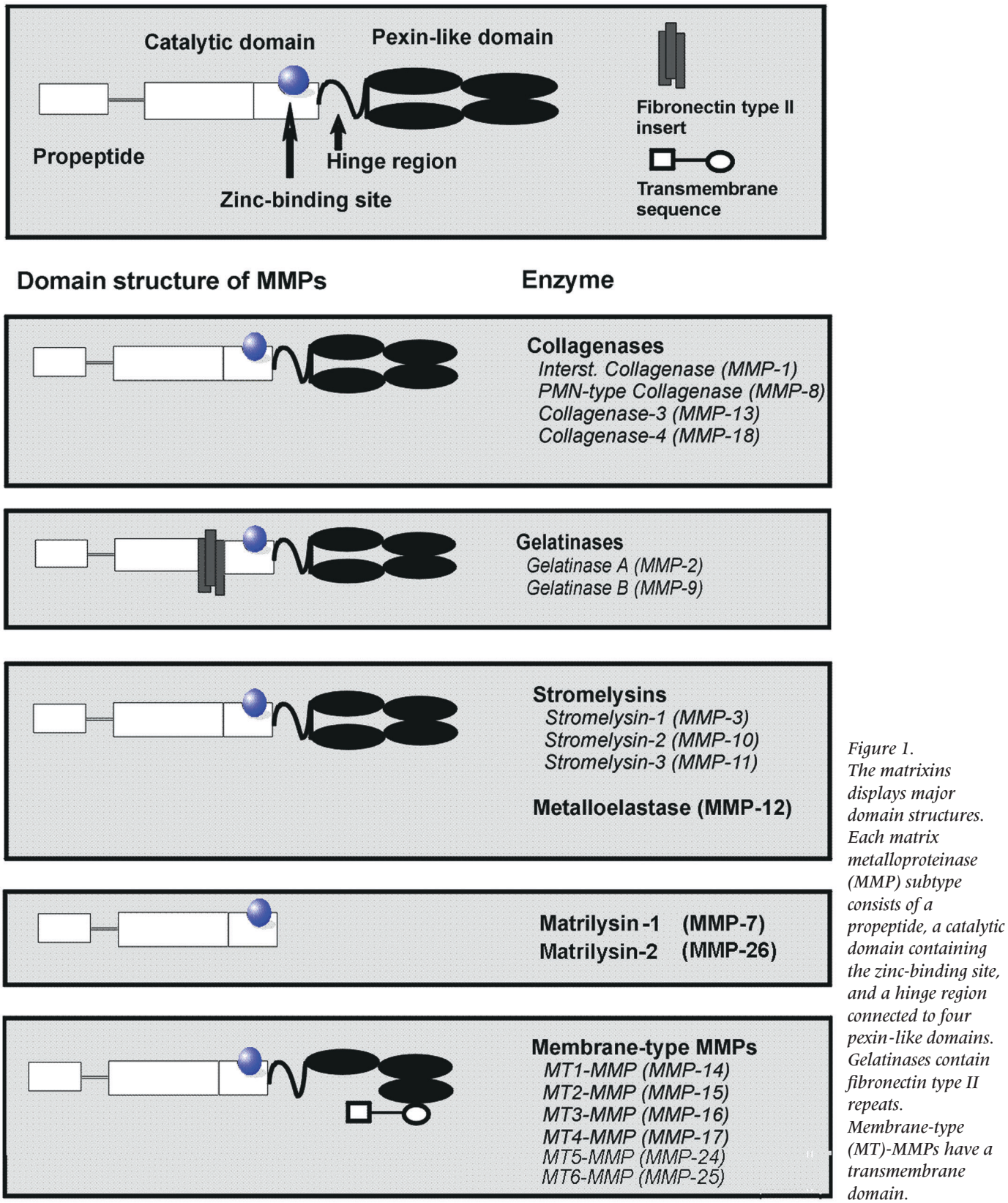

Figure 1.
The matrixins displays major domain structures. Each matrix metalloproteinase (MMP) subtype consists of a propeptide, a catalytic domain containing the zinc-binding site, and a hinge region connected to four pexin-like domains. Gelatinases contain fibronectin type II repeats. Membrane-type (MT)-MMPs have a transmembrane domain.

membrane-bound endopeptidases which degrade important structural proteins. MMPs generally consist of a prodomain, a catalytic domain, a hinge region, and a hemopexin domain *(Figure 1)*. The catalytic domain, which contains the active Zn^{2+} and stabilizing Ca^{2+}-binding site, is required for proteolytic activity and for membrane binding.[15] Proteolytic properties of these enzymes are controlled by transcriptionally regulated protein synthesis as well as by posttranslational modification of the synthesized proteins. Most MMPs are constitutively expressed in vitro at low levels by different cell types, such as keratinocytes, fibroblasts, macrophages, endothelial cells, mast cells, eosinophils, and neutrophils.[16,17]

The first MMP discovered was a collagenase in the tail of a tadpole undergoing metamorphosis. To date, different vertebrate MMPs have been identified, of which 23 are found in humans. MMPs are also found in sea urchin,[18] Hydra,[19] and Arabidopsis.[20] The sequence homology with collagenase 1 (MMP-1), the zinc-binding motif HEXGHXXGXXH in the catalytic domain, and the cysteine switch motif PRCGXPD in the propeptide that maintains MMPs in their zymogen form (proMMP) are the signatures used to assign proteinases to this family. The only exception is MMP-23, which lacks the cysteine switch motif. However, the amino acid sequence of the catalytic domain is related strongly to MMP-1. To date, the MMP family consists of several structurally related members, which can be classified according to the primary structure and substrate specificity into distinct subgroups of collagenases, gelatinases, stromelysins, and membrane-type matrix metalloproteinase (MT-MMP).[12] On the basis of substrate specificity, sequence similarity, and domain organization, vertebrate MMPs can be divided into six groups *(Table I)*. MMP-1, MMP-8, MMP-13, and MMP-18 *(Xenopus)* belong to the group of collagenases. The key feature of these enzymes is their ability to cleave interstitial collagens I, II, and III at a specific site three-fourths from the N-terminus. Collagenases can also degrade a number of other ECM and non-ECM molecules.

Gelatinase A (MMP-2) and gelatinase B (MMP-9) belong to a further group named gelatinases. Gelatinases contain three repeats of type II fibronectin domain, which are inserted in the catalytic domain and bind to gelatin, collagens, as well as laminin.[21] They readily degrade the denatured collagens and gelatins. MMP-2, but not MMP-9, digests type I, II, and III collagens.[22,23] Although MMP-2 null mice develop without any apparent abnormality,[24] mutations in human MMP-2 resulting in the absence of active enzyme are linked with an autosomal recessive form of multicentric osteolysis. This disease belongs to a rare genetic disorder that causes destruction and resorption of the affected bones.[25] Stromelysin 1 (MMP-3) and stromelysin 2 (MMP-10) both have similar substrate specificities, but MMP-3 has a proteolytic efficiency higher than that of MMP-10. Besides digesting ECM components, MMP-3 activates a number of proMMPs. The action of MMP-3 on a partially processed proMMP-1 is critical for the generation of fully active MMP-1.[26] MMP-11 is called stromelysin 3. The matrilysins are characterized by the lack of a hemopexin domain. Matrilysin 1 (MMP-7) and matrilysin 2 (MMP-26),[27] also called endometase,[28] belong in this group. Apart from ECM components, MMP-7 digests cell surface molecules such as pro-defensin, Fas-ligand, and E-cadherin. Matrilysin 2 (MMP-26) also degrades a number of ECM components. Membrane-type (MT)-MMPs have a transmembrane domain, which is constituted by a transmembrane sequence in the carboxy-terminal. They have short spanning domains and a cytoplasmic tail downstream of the hemopexin domain. To date six membrane-type MMPs (MT-MMPs) have been identified. Four membrane-type MMPs are type I transmembrane proteins (MMP-14, MMP-15, MMP-16, and MMP-24), and two are glycosylphosphatidylinositol (GPI) anchored proteins (MMP-17 and MMP-25). With the exception of MT4-MMP, they are all able to activate proMMP-2. These enzymes can also degrade a number of ECM molecules, and MT1-MMP shows collagenolytic activity on type I, II, and III collagens.[29] During postnatal development, MT1-MMP null mice exhibit skeletal abnormalities, since these mice probably lack collagenolytic activity.[30] MT1-MMP plays an essential role in angiogenesis.[31] MT5-MMP is brain-specific and is mainly expressed in the cerebellum.[32] MT6-MMP (MMP-25) is expressed almost exclusively in peripheral blood leukocytes and in anaplastic astrocytomas and glioblastomas, but not in meningiomas.[33,34] Seven MMPs are not classified in the above categories. Metalloelastase (MMP-12) is mainly expressed in macrophages[35] and is essential for macrophage migration.[36] Besides elastin, it degrades a number of other proteins.

MMP-19 was identified by cDNA cloning from liver[37] and as a T-cell–derived autoantigen from patients with rheumatoid arthritis.[38] Enamelysin (MMP-20), which degrades amelogenin, is located within newly formed tooth enamel. MMP-22 was first cloned from chicken fibroblasts,[39] and a human homologue has been identified on the basis of EST sequences. However, the function of this enzyme is still unclear.

The so-called cysteine array MMP (MMP-23) is mainly expressed in reproductive tissues.[40] This enzyme lacks the cysteine switch motif in the prodomain and the

TABLE I

Subtype of MMPs	MMP No.	Substrates and function
Collagenase		
Interstitial collagenase	MMP-1	type I, II, III, VI, and X collagens, entactin, and aggrecan
Neutrophil-collagenase	MMP-8	type I, II, and III collagens, aggrecan
Collagenase-3	MMP-13	type I, II, and III collagens
Gelatinases		
Gelatinase A	MMP-2	type I, IV, V, VII, X, and XI collagens, fibronectin, laminin, aggrekan, elastin, tenascin C, and vitronektin
Gelatinase B	MMP-9	type IV, V, XIV collagens, aggrecan, elastin, entactin and vitronectin
Stomelysins		
Stromelysin-1	MMP-3	aggrecan, fibronectin, laminin, type III, IV, IX, and X collagens, tenascin C, and vitronectin
Stromelysin-2	MMP-10	aggrecan, fibronectin, and type IV collagen
Stromelysin-3	MMP-11	fibronectin, laminin, type IV collagen, aggrecan
Membrane-type MMPs		
MT1-MMP	MMP-14	activator of proMMP-2, type I, II, III collagens, fibronectin, laminin-1, and vitronectin
MT2-MMP	MMP-15	activator of proMMP-2, fibronectin, tenascin, aggrecan
MT3-MMP	MMP-16	activator of proMMP-2, type III collagen, fibronectin
MT4-MMP	MMP-17	unknown
MT5-MMP	MMP-24	activator of proMMP-2
MT6-MMP	MMP-25	type IV collagen, gelatin, fibronectin, fibrin
Other MMPs		
Matrilysin-1	MMP-7	aggrecan, fibronectin, laminin, type IV collagen, elastin, entactin, tenascin, and vitronectin
Matrilysin-2	MMP-26	type IV collagen, fibronectin, fibrinogen, and gelatin
Metalloelastase		
Metalloelastase	MMP-12	elastin, type IV collagen, fibronectin, laminin, vitronectin, proteoglycan
Enamelysin	MMP-20	aggrecan, cartilage oligomeric matrix protein (COMP)
Epilysin	MMP-28	unknown
No trivial name	MMP-19	aggrecan, cartilage oligomeric matrix protein (COMP)

Table I. Selected substrates of different matrix metalloproteinases (MMPs). Interstitial collagenases cleave preferentially different interstitial collagen subtypes. Stromelysins digest basement membrane proteins as substrates, whereas gelatinases process primarily cleaved matrix proteins into smaller fragments.

hemopexin domain. Instead, it has a cysteine-rich domain followed by an immunoglobulin-like domain. Epilysin (MMP-28) is the latest addition to the MMP family, which mainly is expressed in keratinocytes.[41,42] Expression patterns in intact and damaged skin suggest that MMP-28 might function in tissue hemostasis and wound repair.[41-43] MMPs are induced at transcriptional level by a variety of mediators such as interleukin-1 and –6 (IL-1 and IL-6), tumor necrosis factor α (TNF-α), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor-β (TGF-β).[44]

Stepwise proteolytic activation

Proteolytic activation of MMPs is stepwise and it may have evolved to accommodate finer regulatory mechanisms to control destructive enzymes.[45] MMPs are secreted in catalytically latent forms which are subsequently activated in the pericellular and extracellular environment. MMPs can be activated by proteinases or in vitro by chemical agents,[45] such as thiol-modifying agents ($HgCl_2$, 4-aminophenylmercuric acetate, and *N*-ethylmaleimide), oxidized glutathione, chaotropic agents, SDS, and reactive oxygens. There is accumulating evidence indicating the major activation step to be based on the formulated "cysteine switch hypothesis."[45] Upon activation, the Zn^{2+}-binding site is converted to a catalytic propetide. Proteolytic attack on the propeptide domain destabilizes the Cys-Zn^{2+} bond and leads to a spontaneous opening of the switch. The stepwise process of MMP activation by loss of the propeptide region may be initiated by exogeneous proteolytic cleavage.[46] Activation of interstitial collagenases (MMP-1), stromelysin-1 and -2 (MMP-3 and MMP-10), matrilysin (MMP-7), and gelatinase B (MMP-9) can be initiated by plasmin, kallikreins, cathepsins B or G, or by an autocatalytic process.[47] Investigations of proMMP-3 activation with a mercurial compound have indicated that the initial cleavage occurs within the propeptide. This reaction seems to be intramolecular rather than intermolecular.[48] The subsequent removal of the rest of the propeptide is due to intermolecular reaction of the generated intermediates.[48,49] Importantly, activation of specific MMPs also occurs by the plasminogen activation system in vivo.[50] Plasmin is generated from plasminogen by tissue plasminogen activator bound to fibrin and urokinase plasminogen activator bound to a specific cell surface receptor. Both plasminogen and urokinase plasminogen activator are membrane-associated, thereby creating localized proMMP activation and subsequent ECM turnover. Plasmin has been reported to activate proMMP-1, proMMP-3, proMMP-7, proMMP-9, proMMP-10, and proMMP-13.[51]

ProMMP-2 is not readily activated by proteinases. Activation of proMMP-2 and proMMP-13 can be initiated by a cell-bound MT-MMP-complex,[52-54] which includes MT1-MMP, MT2-MMP,[55] MT3-MMP,[56] MT5-MMP,[57,58] and MT6-MMP.[33] MT4-MMP does not activate proMMP-2. The main activation of proMMP-2 takes place on the cell surface and is mediated by MT-MMPs.[59] The unique aspect of this activation step is that it requires the assistance of the inhibitor TIMP-2.[52,60,61] ProMMP-2 forms a tight complex with TIMP-2 through their C-terminal domains, therefore permitting the N-terminal inhibitory domain of TIMP-2 in the complex to bind to MT1-MMP on the cell surface. The cell surface–bound proMMP-2 is then activated by an MT1-MMP that is free of TIMP-2.

Inhibition of matrix metalloproteinases

Natural inhibitors of MMPs are multifunctional proteins with both MMP inhibitor activity and cell growth modulating properties. This group of related, endogenous inhibitors are known as tissue inhibitors of metalloproteinases (TIMPs). Distinct TIMP molecules have been isolated, cloned, sequenced, and characterized from several species.[62-65] TIMPs are specific inhibitors that bind MMPs in a 1:1 stoichiometry, and MMPs form predominantly binary, inhibited non-covalent complexes with their TIMPs.[66] At present, four TIMPs (TIMP-1, TIMP-2, TIMP-3, and TIMP-4) have been identified in vertebrates.[5] TIMPs have 12 identically conserved cysteine residues forming six disulfide bonds which confer marked stability to the molecules. TIMPs (ranging from 21 to 29 kDa) have an N-and C-terminal domain.[67] The N-terminal domain folds as a separate unit and is capable of inhibiting MMPs.[68] A two-domain structure of three loops each can be delineated, and it could be shown that the N-terminal three loops can fold independently and function as an efficient inhibitor of most MMPs. Under the pathological conditions associated with unbalanced MMP activities, changes in TIMP levels are considered to be important because they directly affect the level of MMP activity. TIMPs inhibit all MMPs tested so far, except that TIMP-1 fails to inhibit MT1-MMP.[69] The inhibitory property of TIMP-3 is different from the rest, inasmuch as it inhibits A disintegrin and metalloproteinase (ADAM 17) (TNF-α converting enzyme, TACE),[70] ADAM-10,[71] ADAM-12,[72] and the aggrecanases (ADAMTS-4 and ADAMTS-5).[73] Another unique feature of TIMP-3 is that it binds tightly to sulfated glycosamino-

glycans.[74] A possible role for TIMP-3 heart failure was observed with a reduction in the levels of TIMP-3, corresponding with adverse matrix remodeling in a cardiomyopathic hamster model and in the failing human heart.[75]

Venous ulcer formation

Lipodermatosclerosis is associated with patients suffering from venous circulatory disorders of the lower limbs. Lipodermatosclerosis is the preceding stage of venous leg ulcers, and is associated with a combination of skin changes seen in venous hypertension.[76,77] Long-term inflammation results in scarring and induration of the skin, which resembles scleroderma. The woody hardening of the skin is located on the medial aspect of the leg. Within lipodermatosclerosis there can furthermore be areas of atrophie blanche, which are ivory-white sclerotic plaques. Liposclerotic lesions can surround venous ulcerations, thereby displaying a close relationship between both clinical entities. Characteristically ongoing subcutaneous fibrosis and sclerosis in lipodermatosclerosis lead to a constriction of the mid-portion of the leg. Extensive sclerosis can finally end in the affected leg resembling an inverted bottle, in contrast to lipodermatosclerosis, which shows specific histologic alterations of the epidermal and dermal layer. The main histological features of lipodermatosclerosis are loss of papillary structures in the dermal-epidermal junction zone, dermal pericapillary fibrin cuffs, and fibrosis of the reticular epidermal and partly cellular and matrix tissue components.[6] Venous leg ulcers, in contrast, are characterized by total loss of epidermal and partly dermal cellular matrix tissue components. In spite of many attempts to understand the underlying pathophysiology of venous ulceration, there has been no clear explanation for these major and drastic progressive tissue changes. Analysis of venous ulcer exudates revealed elevated expression and activation of different subtypes of MMPs.[17,78,79] Through their ability to degrade important matrix proteins, MMPS have been considered having a major implication in maintaining venous ulceration by impairing wound healing.[78,46] We showed that different subtypes of MMPs are expressed and activated in lesional skin of lipodermatosclerosis.[80] Our investigations provide evidence of these enzymes having important pathogenic implications in forming venous leg ulcers. Despite collagen bundles being packed densely in lipodermatosclerosis, there is evidence of ongoing collagen digestion by proteolytic active MMP-1 and gelatinase A (MMP-2). Elevated expression on mRNA- and protein levels of MMP-1, MMP-2, and TIMP-1 can be proven in liposclerotic tissue. TIMP, which inhibits preferentially MMP-2 does not show elevated expression in comparison with controls. Currently, the mechanisms initiating the imbalance between MMP-2 and TIMP-2 in lesional skin of lipodermatosclerosis are not known. Enhanced proteolytic MMP-2 activity can be demonstrated in liposclerotic lesions. Obviously, the clinical impression and the histological findings of skin hardening with elevated collagen deposition as described previously stand in sharp contrast to the dynamic picture presented in the fibrotic stage of lipodermatosclerosis.

Consistently ongoing proteolytic processes in lipodermatosclerosis can be demonstrated by activated components of the plasminogen activation system. Earlier there had already been evidence of lipodermatosclerosis being linked to fibrinolytic abnormalities. Jarret et al showed, that patients with lipodermatosclerosis revealed increased plasma levels of D-dimer, D-monomer, and fibrin monomer.[81] Apart from fibrosis of the reticular dermis, important histopathological characteristics of lipodermatosclerosis are dermal pericapillary fibrin cuffs. In spite of their well-organized structures containing (apart from fibrin) fibronectin type I and type III collagens,[6] they had often been accused of being responsible for impaired gas and nutrient exchange between capillary vessels and dermis. Recently, we found that the urokinase-type plasminogen activator (uPA) and its receptor (uPAR) were highly expressed in fibrin cuffed vessels of patients with lipodermatosclerosis and with venous ulcerations. Binding of the uPA to its receptor (uPAR) accelerates plasminogen activation.[82] The fibrinolysin plasmin itself degrades a variety of ECM components, which constitute perivascular fibrin cuffs. In addition, plasmin is known to be an important activator of several MMPs. Mazzieri and coworkers provided evidence of MMP-2 activity being controlled by components of the plasminogen activation system.[50] Therefore, it is tempting to speculate that enhanced proteolytic MMP-2 expression is based on plasminogen activation in lipodermatosclerosis. Plasminogen activation could be interpreted as beneficial, since its target seems to consist of restoring nutrient and oxygen exchange, which is heavily impaired by pericapillary cuffs built up of matrix substrates for fibrinolysin plasmin.[6] Uncontrolled activation of MMPs due to preceding activation of the plasminogen activation system could have implications on the dynamic balance of matrix synthesis and breakdown. Ulcer formation, therefore may be favored by enhanced turnover of the ECM mediated by unrestrained activity of specific MMPs.

Matrixins - repair and prolonged venous ulcer healing

Healing of venous leg ulcers requires properly controlled reepithelialization, angiogenesis, and matrix deposition. Delayed reepithelialization and persistant epithelial defects are typical features of chronic venous ulcers, which barely heal. Failure of reepithelialization appears to be due not to inadequate cell proliferation, but to the impaired capacity of keratinocytes to migrate across the wound bed and form stable attachments to the underlying stromal layer to tissue.[46] There is mounting evidence that misregulation of MMP activity and TIMP-mediated counterregulation contributes to impaired and prolonged wound healing of venous ulcers. However, the pattern of expression of MMPs during venous ulcer healing has to be observed in a more detailed manner. Spatially and temporally controlled expression of several distinct MMPs appears to be associated with different repair phases of venous ulcers. Interstitial collagenase (MMP-1), MMP-2, and MMP-10 are consistently expressed by migrating keratinocytes that move off the basement membrane *(Figure 2)*. Synthesis of these MMPs by migrating keratinocytes may help in dissociating the cell from the collagenous dermal matrix and promote efficient locomotion over dermal and provisional matrices. Keratinocytes use MMP-1 to cleave collagen to gelatin, thereby providing a substrate that is more conducive to migration.[83] Several investigations have demonstrated a key role for altered cell-matrix interactions, particularly contact with type I collagen, in initiating keratinocyte MMP-1 synthesis.[84] The expression of MMP-1 is diminished if reepithelialization is completed. By modulating the amount of intracellular calcium, the MMP-1 expression can be blocked in keratinocytes which have migrated away from the basal membrane.[85]

Furthermore, MMP-3 and MMP-10 are secreted by basal keratinocytes in chronic venous ulcers.[17] However, only a distinct population of cells is able to express these specific metalloproteinases. MMP-3 is expressed at a distance from the wound edge and is probably not required for the process of reepithelialization, but for restructuring the newly formed basement membrane. Since MMP-3-positive keratinocytes reside on an intact basement membrane, the primary stimulus for production may be soluble mediators such as IL-1, TNF-α, EGF, PDGF, or TGF-β.[16] MMP-10 displays a coexpressional pattern with MMP-2 at the epithelial tip bordering venous leg ulcers. This endopeptidase may be involved in the activation step of the interstitial collagenase (MMP-1). MMP-2 may hereby facilitate keratinocyte migration by degrading noncollagenous matrix molecules.[17] During wound repair, both MMP-1 and MMP-3, but not MMP-10, are expressed in dermal fibroblasts and participate in the formation and removal of granulation tissue and resolution of scar tissue. The number of cells expressing MMP-1 and -3 in the stromal tissue is greater than the number of positive cells in normally healing wounds. Collagenase-3 (MMP-13) is not expressed by keratinocytes bordering normally healing wounds. In fact, MMP-2 and MMP-13 are abundantly expressed by stromal cells in chronic wounds distinct from areas of stromal MMP-1 expression. Human skin fibroblasts cultured in a three-dimensional collagen gel also express MMP-13. In contrast, dermal fibroblasts cultured on tissue culture plastic do not, indicating an important role for cell-matrix interactions in the control of MMP-13 expression in fibroblasts. While MMP-1 is critical for reepithelialization, MMP-13 is involved in the degradation of type I and III collagens and their cleavage products in the chronic venous leg ulcer bed may therefore play a

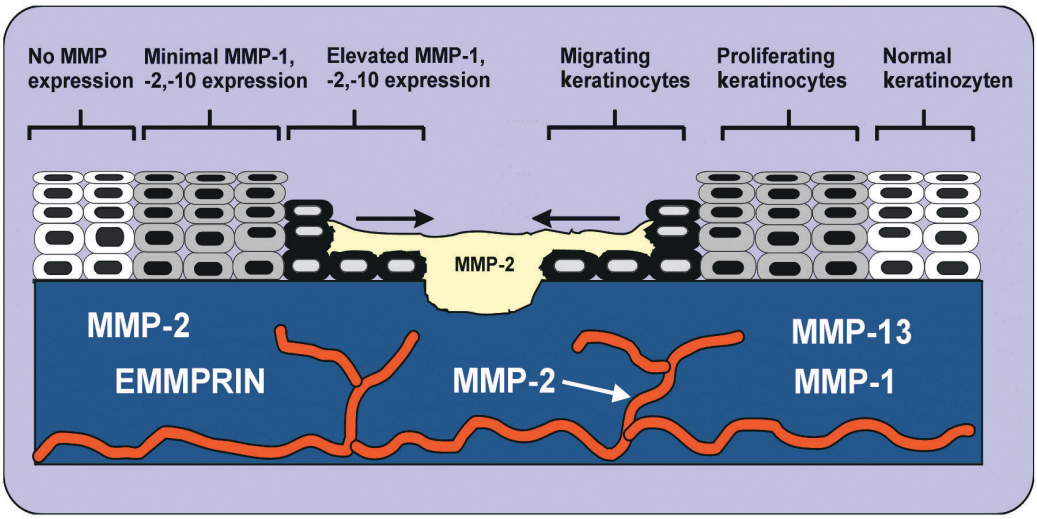

Figure 2. Pattern of matrix metalloproteinase (MMP) expression in wounded dermis of venous leg ulcers. Interstitial collagenase-1 (MMP-1), MMP-2, and MMP-10 are prominently expressed by migrating basal keratinocytes. Furthermore, MMP-3 is expressed at sites of disrupted basement membrane of basal keratinocytes at a distance from the wound edge. Fibroblasts in dermis also secrete different subtypes of MMPs: MMP-1, MMP-2, and MMP-13.

pivotal role in the pathogenesis of chronic ulcers.[46] Recently, we provided evidence of intense staining for EMMPRIN, MT1-MMP and MT2-MMP in dermal structures of venous leg ulcers, whereas only EMMPRIN is expressed in perivascular regions. Our findings indicate that venous leg ulcers are characterized by elevated expression of EMMPRIN, MT1-MMP, and MT2-MMP. The immunohistological findings of skin alterations also indirectly reflects the dynamic process of activation of soluble and membrane-bound MMPs, which may be highly induced by EMMPRIN in venous leg ulcers.[86]
Inhibitors of metalloproteinases play a crucial role in the remodeling process of venous ulceration. A sudden disruption of the balance between proteinase activity and inhibitor level may deteriorate wound healing. TIMP-1 is spatially and temporally regulated during venous ulcer healing. In comparison with acute wounds, nonhealing venous ulcers contain high levels of activated gelatinases and low levels of TIMP-1.[78,79] Lack of TIMP-1 expression in keratinocytes of chronic ulcers in comparison with normally healing wounds suggests that excessive proteolysis retards the healing of venous ulcers.[65] Epidermal TIMP-1 may inhibit proteolytic active metalloproteinases from degrading the epidermal basement membrane, thereby representing a protecting role.

Among other proteases, there had been evidence of the neutrophil elastase being upregulated during acute wound healing and that an abnormality in downregulation of this protease could be partially responsible for the transition to chronic wound healing states in the aged.[87] In light of these observations of elevated protease activity of chronic wound fluid, there had been also evaluations with regard to the stability of growth factors and their receptors in chronic wound fluids.[88] Specific growth factors had been shown to be destroyed by fluid samples from chronic wounds. Furthermore, there had been accumulating evidence that in wound fluids of venous leg ulcers MMP-1 and MMP-2 are strongly activated. These proteases are also expressed and activated in stromal tissue of the wound bed in leg ulcers. These data indicated that MMPs play a dual role in chronic venous leg ulcers. On the one hand, they are essential components during the phase of reepithelialization, and on the other hand elevated degradation due to activated matrixins in the wound fluid, as well as in the wound bed, significantly prolong wound healing in venous leg ulcers. Therefore, antagonizing matrixins in venous leg ulcers must take into account the fact that these proteinases are distinctly spatially and temporally expressed and activated.

Future treatment modalities

Pharmaceutical research into antagonizing MMPs progressed in the past few years. Inhibition analysis of MMPs using MMP inhibitors has been performed in different diseases such as neurodegenerative and cardiovascular diseases, corneal ulcers, osteoporosis, rheumatoid arthritis, dysfunctional uterine bleeding, T-cell-mediated tissue injuries, inflammatory bowel diseases, Crohn´s disease, and host-versus-graft disease.[47] In spite of efforts in the development of MMP inhibitors, limited bioavailability and a lack of enzyme selectivity have hindered a quicker progression. Earlier inhibitors were designed relying upon sites of substrate cleavage. They were peptidomimetic, with the hydroxamic acid moiety replacing the terminal carboxylic acid of the corresponding peptide cleavage product. Unfortunately, these inhibitors lacked good bioavailability, and displayed little specificity for individual MMPs. Hydroxamic acid inhibitors are rapidly metabolized by the liver and require frequent dosing to maintain therapeutic plasma drug levels. In the mean time, progression in pharmacokinetic profiles has allowed the design of nonpeptidic inhibitors.[89-94]
Application of TIMPs as a therapeutic tool for cardiovascular disease and cancer through gene therapy or direct protein application is still in the early phase of development.[95] There is a clear potential for the application of TIMPs as endogenous inhibitors, especially because the results of clinical trials with small molecule inhibitors have been disappointing.[96] Adenoviral overexpression of TIMP-1 in a mouse model of atherosclerosis showed a reduction in the lesion.[97] Local expression of TIMP-1 in a rat model of aneurysm prevented aneurysm degradation and rupture.[98] However, expressing wild-type TIMPs could have drawbacks because multiple MMPs may be inhibited, and in the case of TIMP-3, ADAMs and ADAMTSs may be inhibited as well. Probably the best way to achieve success will be the development of engineered TIMPs with altered specificity, to allow targeting of specific proteinases. To date, there have been no studies analyzing the effect of specific inhibitors of metalloproteinases in venous leg ulcers. Reasons limiting the general application may rely upon its poor bioavailability. It is conceivable that local application of selective compounds of MMP inhibitors may have a beneficial effect on the early phase of wound healing in venous ulcers. Success in the clinical application of MMP inhibitors in the near future might also challenge clinical investigations in the field of wound healing.

CONCLUSIONS

MMPs are important enzymes in many biological and pathological processes, due to their ability to degrade ECM components. This review provides new insight into the interplay between cells, the ECM, and its catabolism in venous leg ulcers. Considerable progress has been made in the understanding of biochemical aspects of MMPs in the last decade, including their activation and catalytic mechanisms, substrate specificity, and the mechanism of inhibition by TIMPs. However, there are important questions that remain unresolved. In spite of the fact that collagenase was the first member of the family to be discovered, the mechanism by which collagenases cleave triple-helical collagens is not fully understood. An explanation as to how TIMP-3 inhibits metalloproteinases of the ADAM family awaits future experimental studies. Progress in structural analyses has led to the design of synthetic metalloproteinase inhibitors, some of which have exhibited efficacy in animal models. In contrast, clinical trials have unfortunately often shown no significant benefit in humans. Such discrepancies may be due to the fact that those trials were conducted in patients at advanced stages of the disease. Another possibility is that the inhibitor concentration reached in vivo was insufficient to inhibit target enzymes in the tissue, or that nontarget enzymes were inhibited. However, it is conceivable that these trials did not take into account the fact that matrixins are distinctly spatially and temporally expressed and activated. The design of specific inhibitors of matrixins is an important future challenge. Such inhibitors are useful not only for gaining insights into the biological roles of MMPs, but also for the development of therapeutic interventions for diseases associated with unbalanced ECM degradation. An outstanding example of such a disease is venous leg ulceration. In this review, different investigations, including our own experiments, were discussed, which suggest a pivotal role of matrixins in the continuum of processes linking ulceration and repair. What remains to be learned is the exact role of these proteinases in different compartments of tissue. It might be that genetics will help to provide answers to these questions - specifically transgenic mouse technology. Mice that inappropriately express MMPs which have been engineered to eliminate matrixins both help in this regard. Transgenic mice are complex systems; however, it can be difficult to fully understand the molecular mechanism leading to a phenotype, despite the fact that alteration was made in only a single gene. Therefore, it will be necessary to combine different genetic studies. A number of pharmaceutical companies are working in the field of inhibitor development, the inhibitor being administered systemically. Approaches to inhibit MMP activity, besides direct targeting of the enzyme´s active site, still seem important to consider for the healing of venous leg ulcers. One likely possibility could be inhibiting MMP activity indirectly by targeting MMP synthesis. Understanding the molecular pathway of matrix degradation by proteolytic enzymes of MMPs may facilitate finding potential therapeutic strategies in managing patients with advanced complications of chronic venous insufficiency.

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Address for correspondence
Priv-Doz. Dr med Yared Herouy
Department of Dermatology
University Medical School
Hauptstr. 7
D-79104 Freiburg - Germany
Tel: +49-761-270-6710
Fax: +49-761-270-6720
e-mail: *herouy@haut.ukl.uni-freiburg.de*

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Classification of primary varicose veins of the lower extremities: a consensus statement from Latin America

Roberto SIMKIN *(Argentina)*
Jorge ULLOA *(Colombia)*
Co-Chairmen

Michel Loustric (France)
Coordinator

FACULTY

Hector CALDEVILLA (Argentina)
Mario H. GENERO (Argentina)
Newton de BARROS, Jr. (Brazil)
Almeida R. HAMILTON (Brazil)
R. MOURA (Brazil)
Raul POBLETE (Chile)
Jorge FERNANDEZ-DIEZ (Mexico)
Marcelo PARAMO DIAZ (Mexico)
Luis SIGLER (Mexico)
J. Leonel VILLAVICENCIO (Mexico-USA)

Cuernavaca, Mexico, February 1998
Miami, Florida. January 1999

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INTRODUCTION

This document is the result of two consensus conferences organized with the collaboration of a group of specialists representing several Latin American countries, who met with the purpose of establishing a classification of primary varicose veins. The Latin American Consensus Committee (LACC) met for the first time in Cuernavaca, Mexico, in February 1998 and almost a year later in Miami, Florida, in January 1999. Among the participants were members of the Pan-American Society of Phlebology and Lymphology, International Union of Phlebology, World College of Vascular Diseases, the American Venous Forum, and the Latin American Venous Forum (LAVF). The conferences were supported by an educational grant from the Institut de Recherches Internationales Servier. Disciplines involved in the study of venous diseases and its complications were well represented among the members of the Faculty: Epidemiology, Pharmacology, Genetics, Dermato-pathology, Physiology, Angiology, and Vascular Surgery. The different aspects and characteristics of primary varicose veins were thoroughly discussed. The present report represents the consensus of the participants at the meetings.

THE PROBLEM

Venous diseases are one of the most common problems encountered in medical practice throughout the world. The members of the LACC specifically focused on obtaining information about the prevalence of chronic venous insufficiency (CVI) in Latin America, and in developing a simple, easy-to-understand, and easy-to-use classification of primary varicose veins.

The scarce regional reports available at the present time[1,2] suggest that similar to what occurs in Europe and other countries, CVI in Latin America has a high prevalence in individuals of both sexes, and produces a range of clinical manifestations that may lead to different degrees of disability.[3] Varicose veins occur in about 30% of females and 15% of adult males.[4-17]

In an epidemiologic study of varicose veins, Brand reported an incidence of varicose veins per year of 1.9% in men and 2.6% in women.[15] The prevalence of venous diseases has stimulated various organizations to form consensus groups to study, in a systematic manner, the impact and consequences of the disease, not only on the quality of life of the patient, but also on the high cost to society caused by the loss of work and disability. Hume, in his Presidential Address to the American Venous Forum, reported that the annual cost of CVI

in the United States is approximately 1 billion dollars.[16] Like the care provided for leg ulcers, varicose veins are treated predominantly by physicians. However, due to their prevalence, there is a current trend among several medical specialists, such as dermatologists, phlebologists, and angiologists, to include varicose veins within the scope of their specialty. The care of varicose veins represents a considerable overload in surgical care in a hospital. This had led to the development of outpatient clinics where patients can be operated on and discharged a few hours after the procedure. Ambulatory venous surgery has been performed for many years in a safe and effective manner.[18-20] These procedures have lowered the cost of varicose vein surgery and decreased the surgical caseload of the general surgical training programs.

From the outset, the goal of the LACC was to develop a classification of primary veins of the lower extremity. Why should we add another classification to the ones currently known? All the current classifications have advantages and disadvantages. Some of them are too simple and others are too complicated. There is no unanimous acceptance of any classification. We reviewed all the published classifications, including the most recent.[21,22] The most thorough classification of chronic venous disease was the result of the Consensus Committee of the American Venous Forum that met in Maui, Hawaii, in February 1994. The deliberations of the Committee produced the Clinical, Etiologic, Anatomic and Pathophysiologic (CEAP) Classification. The latter was prepared with the aim "to present a more precise classification of chronic venous dysfunction which is simple enough to encourage its universal acceptance." The classification of venous disorders of the extremity was based on their clinical, etiologic, anatomic, and pathophysiologic (CEAP) characteristics. Despite its thoroughness and objectivity, this classification has often been the subject of criticism for its complexity, which prevents its application in clinical practice and ultimately limits its usefulness to clinical investigation reports. The CEAP classification allows description of CVI only and not grading of the disease. Therefore, grading scales have been further set up.[23,24] The latest one has been recently validated.[25] In this classification, clinical description of CVI has been divided into 7 classes, going from 0 to 6. Varicose veins of the lower extremities are classified as clinical "C" classes 1 or 2. Within the Anatomic classification, telangiectasias are defined as intradermal veins with a diameter of 1 mm or less, reticular veins as intradermal veins measuring 4 mm or less, and truncular veins as subdermal veins greater than 4 mm in diameter. Due to the complexity of the CEAP classification, which at the present time is going through a thorough process of revision, the LACC met in two conse- cutive years to define the impact that CVI produced in Latin America and propose a simple, practical classification of primary varicose veins that does not claim to substitute the CEAP. It is of interest to note that, since 1999, the date of the LACC consensus, several committees have independently met in Europe and in the United States to discuss refinements of the current CEAP classification.[26] It is hoped that the efforts of the LACC be considered as a step in the right direction trying to simplify and refine the clinical segment of C of the CEAP. To achieve this objective, each of the participants was assigned to discuss a particular subject ranging from epidemiology, pharmacology, genetics, dermato-pathology, clinical manifestations, and pathophysiology. These subjects were extensively discussed by the members of the Committee.

CLINICAL CLASSIFICATION OF PRIMARY VARICOSE VEINS

TABLE

A. Telangiectasias:	
	• Localized
	• Diffuse
B. Reticular veins	
	• Localized
	• Diffuse
C. Truncular	
	• Secondary to insufficiency of:
	• Great saphenous vein and tributaries
	• Small saphenous vein and tributaries[24]
	• Perforating veins
	• Other venous systems: gastrocnemius
	Solear
	Pelvic

DEFINITION OF TERMS

- **Primary varicose veins.** Primary varicose veins of the lower extremities are dilated and tortuous veins which function abnormally and whose etiology is largely unknown.[22-34] From the anatomical point of view, the varices may be superficial or deep. Varicose veins may be secondary to insufficiency of the superficial system or to insufficiency of the deep system and some large

perforators. It is recognized that the deep system may be the subject of primary valvular incompetence but the superficial system is the most frequently affected.

- **Telangiectasias** are dilatations of intradermic veins measuring 1 mm in diameter or less. The dimension is 1 mm. They may be localized or diffuse and may be red, purplish, or blue. They are localized most commonly in the thighs, but may affect any other area of the extremity. Often they are present in limbs suffering concomitantly from other types of varicose veins such as reticular or truncular varicosities.
- **Reticular varices** are dilated veins of the dermic [26] plexus measuring from 1 to 4 mm. Depending on their location, their color varies from purplish to blue. They may be localized or disseminated and may be associated with other stages of varicose veins in different territories of the extremity.
- **Truncular varicose veins** are varicosities distributed along the great or small saphenous veins and their tributaries. Their diameter is 4 mm or larger and may be associated with varicose veins of other venous territories such as pelvis and gastrocnemius and soleus muscles. They may be the result of isolated incompetent perforators.

CLINICAL STAGES

Primary varicose veins of the lower extremities can be classified into four clinical stages:

- **Stage 1.** Asymptomatic.
- **Stage 2.** Symptomatic. Edema, heaviness, tiredness, burning sensation, cramps, itching, and pain are the most common symptoms.
- **Stage 3.** Skin Changes I. In this stage, pigmentation, eczema, scaling, and cellulitis are common. These manifestations are usually localized to the distal third of the leg and predominantly on the medial aspect.
- **Stage 4.** Skin changes II. Lipodermatosclerosis and ulceration. Lipodermatosclerosis is an advanced stage of chronic venous insufficiency. It may be present as a result of superficial venous incompetence, either alone or in combination with deep venous insufficiency. The latter may be the result of reflux, obstruction, or a combination of both. The microcirculatory changes and the chronic inflammatory process produce fibrosis and scar tissue which involve skin, subcutaneous tissue, and sometimes fascia and periosteum.
- **Ulceration** is the final stage of either superficial or deep CVI. It is localized preferentially on the medial aspect, distal third of the extremity, even though less frequently it may occur on the lateral aspect of the leg and dorsum of the foot.

COMPLICATIONS

1. **Varicose hemorrahage**
   This is a frequent acute complication in those who suffer from varicose veins. Bleeding may be external or subcutaneous. The hemorrhage may be alarming.

2. **Varicophlebitis**
   Also known as varicothrombosis, it is characterized by the presence of a thrombus in varicose veins, which provokes acute inflammatory clinical manifestations such as pain, redness, swelling, and induration. It generally occurs in the truncular veins.

CONCLUSION

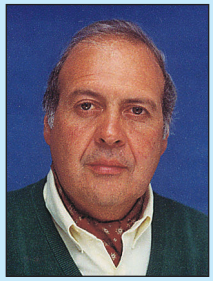
A simple classification enables us to have a common language, and allows us to guide the therapeutic stages in a simple manner. It is simple for the specialist, and understandable for the nonspecialist. Differing from others, this classification, based on descriptive clinical observations, allows us to observe the existence and magnitude of CVI. Using appropriate noninvasive diagnostic techniques, it is possible to confirm the diagnosis and determine the degree of severity of the disease, which is essential for its proper management. The proposed classification is simple and easy to use. It will guide the physician to select the necessary noninvasive diagnostic methods to arrive at a working diagnosis and proper management.

Address for correspondence

Roberto Simkin

Republica Arabe Siria 3166
9th floor
1425 Buenos Aires
Argentina

Fax: +54 11 4805 4774
e-mail: robsim@ciudad.com.ar



Address for correspondence

Jorge Ulloa, Jr, MD

Fundacion Colombiana de Enfermedades Vasculares

Santa Fe de Bogata

Colombia

Tel: +57-1320-2511
Fax: +57-1288-7559
e-mail: *julloa@usa.net*

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Paper presented at the American Venous Forum Congress

Relationship between signs, symptoms, reflux, and quality of life in patients with chronic venous disease

Michel PERRIN, Benoît ARNOULD*

Background: Quality of life (QoL) of patients suffering from chronic venous disease (CVD) has been shown to be globally impaired. Little is known about the individual impact of clinical parameters on the QoL of patients with CVD.

Objective: To assess the impact of demographic data, clinical data, signs, and symptoms on the QoL of patients with CVD.

Methods: *Patients:* Symptomatic patients, diagnosed as CEAP clinical class 0 to 4, aged over 18 years, male or female, of any race, wearing compression stockings or not, were enrolled in the study.

Reflux assessment: Detection by means of pocket Doppler, confirmed by photoplethysmography.

Symptom assessment: Sensation of swelling, cramps, and leg heaviness using a 4-point scale (0 = absent to 3 = severe), pain using a 10-cm visual analog scale (VAS). Edema: By measuring leg circumference.
Quality of Life: Using the Global Index (from 0= bad QoL to 100= excellent QoL) of the CIVIQ questionnaire (20 severity items).

Statistical analysis: A multivariate linear regression model was used to assess the specific contribution of each factor to the level of QoL.

Results: The database included 3516 observations for which the clinical and the QoL data were completed. Patients were mostly Caucasian (77.9%), female (81.1%), with mean age 45.5±12.3 years, mean BMI 26.1±6.47, mean duration of CVD 12.4±9.8 years. Venous reflux was found in 46.6% and CEAP distribution C0s-C1 in 21.1%, C2 in 40.5%, and C3-4 in 36%.
Age, female gender, BMI, ankle perimeter, presence of reflux, and assignment to a severe CEAP clinical class had a slight impact on QoL, with minor change in the CIVIQ global score. In contrast, symptoms, particularly heaviness and pain, were found to seriously affect patients' QoL. *(Table I)*

Conclusion: This study demonstrates that symptoms usually attributed to CVD are the factors with the most negative influence on the patients' QoL. This suggests that a treatment reducing symptoms might improve the QoL of symptomatic patients, even in the absence of detectable reflux or signs.

Perrin M, Arnould B. Relationship between signs, symptoms, reflux, and quality of life in patients with chronic venous disease. Paper presented at the American Venous Forum Congress.

Symptoms and quality of life: a serious and significant relationship

I - EARLIEST SYMPTOMS OF CVI: A VERY DISABLING QUALITY OF LIFE

Chronic venous insufficiency (CVI) is a serious clinical condition affecting a large number of people, and is important both from an epidemiological point of view, and on account of its socioeconomic repercussions.[1] In the Western world, the consequences of the high prevalence of CVI are well known, as are the costs of diagnostic procedures and treatment programs as well as the significant amount of working hours lost and the repercussions on quality of life.[2-4]

A specific questionnaire for CVI (CIVIQ) has been in use since 1992, with surprising results for a disease that has hitherto been so severely underestimated.[5] CVI has a profoundly negative effect on patients, daily life and the results illustrate the impact of CVI on morbidity. In addition, in the French survey by Levy in 2002, 53% of CVI patients considered that venous symptoms severely impaired their quality of life.[6]

CVI leads to serious phlebological repercussions and also physical and social consequences in the daily life of CVI patients. Pain and leg heaviness are causes of sensation of fatigue.[5]

Table I. CVI symptoms have the most negative influence on quality of life
Results of multivariate analyses

Independent factor	Attributable in the qualify of life global score*	*P* value
Heaviness (severe/absent)	-19.75	<0.0001
Pain (3.69 cm on VAS)	-10.0	<0.0001
Sensation of swelling (severe/absent)	-9.92	<0.0001
Nocturnal cramps (severe/absent)	-8.96	<0.0001
Sex (female compared with male)	-5.6	<0.0001
Reflux (presence compared with absence)	-2.27	<0.0001
CEAP (assignment to C4 compared with assignment to C0)	-0.83	<0.0005
Ankle circumference (every additional cm)	-0.14	0.0042
Age (every additional year)	-0.12	<0.0001
BMI (every kg/m^2)	-0.08	0.037

* CIVIQ score

The patients feel very uncomfortable, which can make everyday life more or less difficult: for instance, patients are troubled, and almost limited, while standing for a long time, climbing stairs, crouching, or kneeling. They are also handicapped in their daily life activities, such as working in the kitchen, carrying a child, ironing, cleaning floors or furniture, or doing jobs around the house. They also complain of problems with sporting activities and physically strenuous efforts.

II - QUALITY OF LIFE SIGNIFICANTLY DEPENDS ON SYMPTOMS[7]

(see abstract above)
As demonstrated by this new study which was presented in Orlando at the last American Venous Forum Congress, quality of life is significantly linked to the presence of symptoms *(Table I)*. Surprisingly, the presence of reflux at assignment to a high clinical CEAP class had a slight influence on the quality of life of CVD patients, as for demography (sex, age, ethnic origin). This strongly suggests that a treatment reducing symptoms might improve the quality of life of symptomatic patients, even in the absence of severe signs or reflux.

III - DAFLON 500 mg IMPROVES THE QUALITY OF LIFE OF CVI PATIENTS

The new results presented at Orlando come from a new statistical analysis of the RELIEF study.[8] The primary aim of the RELIEF study was to internationally validate the CIVIQ questionnaire wich appears to be a reliable, sensitive, and clinically valid tool.
The RELIEF study also confirmed the efficacy of Daflon 500 mg in improving quality of life of CVI patients. A significant improvement in quality of life scores was obtained according to dimension and global index in both groups of patients (with and without venous reflux). Psychological, social, physical, and pain dimensions significantly improved with Daflon 500 mg treatment. A sustained improvement was observed from the beginning of the treatment to the end of the study *(Figure 1)*.

Figure 1. Daflon 500 mg significantly improves global index of quality of life score

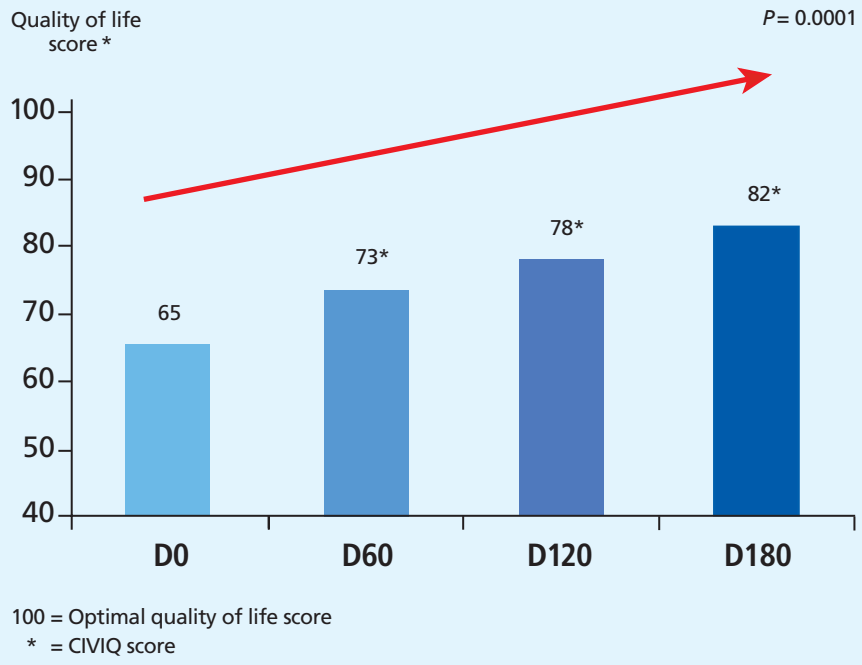

Figure 1. Jantet G, and the RELIEF Study Group. Chronic venous insufficiency: worldwide results of the RELIEF study. Angiology. *2002;53:245-256.*

As regards the global index of CIVIQ, the main improvement was noted after the first 2 months of treatment, and further improvements were observed during each visit until the end of the study *(Figure 1)*. The evolution of the global index of the CIVIQ significantly differed between the two groups (P=0.0001), the group without reflux being less impaired (of 5 points in GIS) than the group presenting reflux.

CONCLUSION

Quality of life of CVI patients has been evidenced to be very impaired due to symptoms such as pain, leg heaviness, itching, and sensation of swelling. The main drive for a patient with CVD to consult a doctor might be the presence of symptoms, even in the absence of reflux or severe signs. Evidence from the RELIEF study indicates that CVI, even "modest" cannot be limited to cosmetic problems. Symptoms that are very often associated with CVI, right from the beginning of the disease, immediately translates into limitations in daily activities.

The quality of life results of the worldwide RELIEF study showed a significant improvement in the patients' QoL with a Daflon 500 mg treatment. This improvement in QoL scores is the logical result of the improvement in all clinical manifestations of CVI by Daflon 500 mg.

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Lymphatic function in severe chronic venous insufficiency

Peter S. MORTIMER,
Ian C. PEARSON

St George's Hospital Medical School, London, UK

SUMMARY

Clinical and laboratory evidence confirm that in chronic venous insufficiency (CVI) there is microangiopathy of the lymphatic network. The resulting lymphatic dysfunction leads to chronic edema which complicates the clinical picture of severe CVI. Optimum management requires measures to improve lymphatic drainage as well as attending to the venous disease. Exercise, elevation, and compression are principles of treatment effective in both pathologies.

ABSTRACT

The veins and lymphatics have a similar embryological origin and anatomy. When pathological changes occur in the venous system, there are microangiopathic changes of both the vascular and lymphatic networks. The loss of lymphatic function allows the development of edema, which is commonly seen in severe chronic venous insufficiency. The edema complicates management, particularly if ulceration has occurred. Management of venous disease and lymphatic dysfunction is based on similar principles of exercise, elevation, and compression.

INTRODUCTION

The lymphatic system is organized into a one-way drainage system to allow re-circulation of tissue fluid, macromolecules and immunologically active cells back to the vascular compartment. If there is excessive demand on the lymphatics, or a congenital or acquired abnormality of the lymphatics, there is a loss of tissue fluid homeostasis. This allows edema to develop, which can be recognized clinically and is a feature of severe chronic venous insufficiency (CVI).

ANATOMY AND PHYSIOLOGY OF NORMAL LYMPHATICS

Evidence exists that the venous and lymphatic systems share a similar embryological origin. The first lymphatics to appear are lymph sacs which arise from nearby major veins. The VEGFR3 gene is found expressed in venous and lymphatic (not arterial) endothelia at 12.5 days of development, but is subsequently only expressed on developing lymphatic vessels, and in the adult on lymphatic endothelia and high endothelial venules.[1]

The lymphatic system is composed of an intradermal network of initial

lymphatics which drain into precollecting lymphatic vessels. The initial lymphatics are blind-ending endothelial tubes with open intercellular junctions, which allow the entry of fluid if the interstitial pressure is greater than the intraluminal pressure. However, these intercellular junctions close if intraluminal pressure exceeds interstitial pressure, avoiding the egress of collected lymph. At this level, fluid movement is effected by local pressure gradients and mechanical forces, such as massage and intermittent contraction of skeletal muscle.[2]

The precollecting vessels drain into muscular collecting vessels running up the limbs in close association with the major blood vessels. These lymphatic vessels are lined by smooth muscle and are intrinsically contractile, in contrast to veins. At this level, the contractility acts as the major source of lymph propulsion.[3] All lymphatic vessels larger than the initial lymphatics possess valves which act to prevent reflux of fluid.

The anatomy of the lymphatic system sets up a one-way drainage system to allow the return of fluid and macromolecules from the interstitium to the circulation to maintain tissue homeostasis. In effect, this is a safety valve preventing interstitial edema. The lymph also contains immunologically active cells such as lymphocytes and macrophages, and antigenic organic material such as bacteria. The recirculation and presentation to lymph nodes of these components means the lymphatic sytem also has a vital immune surveillance role. In the leg, there are superficial and deep lymphatic systems divided by the deep fascia (in parallel to the venous system). The superficial compartment drains to the groin following the course of the long saphenous vein. One to two lymphatic trunks will arise from the heel and follow the course of the short saphenous vein to the popliteal fossa. The deep system drains the muscles, bones, joints, and fascia by trunks running in close association with the deep veins.

THE ROLE OF THE LYMPHATICS IN NORMAL TISSUE FLUID HOMEOSTASIS

The traditional view is that most of the filtrate provided by the arterial capillaries is continuously reabsorbed by the downstream venous microvessels where pressure is normally low, leaving behind a small concentrated fraction of the original filtrate to drain away as lymph. There is now considerable evidence against this concept. In the steady state, combined interstitial hydrostatic and osmotic pressures measured directly in the human arm never reached levels sufficient to overcome filtration.[4] These results are just one of many data sets obtained from a variety of tissues and species in which summation of the Starling forces (see below) reveals no net reabsorption in venous capillaries.[5] In most tissues, lymph is produced by a net filtration force that dwindles along the longitudinal axis of the blood capillary. Tissue fluid balance, therefore, depends crucially on lymph flow. In circumstances where capillary pressure is raised, eg, venous hypertension, the role of the lymphatics is even more important.

THE PATHOPHYSIOLOGY OF EDEMA AND VENOUS INSUFFICIENCY

Edema occurs when the rate of production of interstitial fluid exceeds the rate of removal by the lymphatics. In principle:

$dv / dt = J_V - J_L$

dv / dt = the rate of swelling

J_V = net capillary filtration rate

J_L = lymph flow

An increase in capillary filtration will therefore need a concomitant increase in lymph flow to avoid tissue swelling. Most causes of edema are due to the lymph flow being unable to compensate for this increased demand. In primary lymphedema, net capillary filtration is unchanged but lymph flow is compromised.

In venous disease, there is an increase in capillary filtration. The following equation governs capillary filtration:

$$J_V = Lp \cdot S \cdot ((Pc - Pi) - \sigma \cdot (\pi_c - \pi_i))$$

where

Lp = hydraulic conductance of capillary wall

S = surface area for exchange

$Pc - Pi$ = difference between capillary pressure and interstitial pressure

σ = reflection coefficient for plasma proteins

$\pi_c - \pi_i$ = difference between plasma and interstitial osmotic pressures

In venous disease there will be an increase in capillary pressure (Pc) initially. This will be counteracted by:

a) A rise in interstitial pressure due to an increased interstitial fluid volume.

b) A fall in interstitial colloid osmotic pressure due to a dilu-

tion effect, increasing the osmotic effect of plasma proteins in the blood compartment.

Balance is lost if venous insufficiency leads to an overwhelming increase in the capillary pressure. If inflammation occurs concurrently with the venous insufficiency, eg, cellulitis, stasis dermatitis, lipodermatosclerosis, this may lead to an increase in capillary permeability to water (Lp) and proteins (σ) and increased blood flow (further increasing capillary pressure).

When there is a net rise in capillary filtration, the lymphatic system "safety valve" must respond with an increase in lymphatic flow to avoid edema. In venous insufficiency, this has been illustrated by both lymphography and lymphoscintigraphy.[6,7] This is likely to be the main buffering system against edema formation. An anatomical mechanism already present to buffer gravitational fluid loading is the increased lymphatic density and lymphatic transport capacity of the leg in comparison with the arm in healthy subjects.[8]

LYMPHATIC STRUCTURE AND FUNCTION IN SEVERE CHRONIC VENOUS INSUFFICIENCY

In a clinical study of 56 patients with venous ulceration in both community and hospital settings, edema was present in 55% of ulcerated legs. The clinical changes of lymphatic insufficiency, principally an inability to pinch a fold of skin at the base of the second toe (Stemmer's sign), hyperkeratosis, and increased skin creases, were present in 22% of ulcerated legs.[9] This provides clinical evidence that in severe CVI with ulceration, the lymphatics become compromised and edema, eventually with skin changes, supervenes.

Fluorescence microlymphography undertaken in patients with severe CVI compared with healthy controls demonstrated obliteration of parts of the lymphatic superficial capillary network, cutaneous reflux of lymph from deep to superficial channels, and increased lymphatic capillary permeability.[10,11] This is evidence that in CVI there is lymphatic microangiopathy in association with the microangiopathy of blood capillaries.

Quantitative lymphoscintigraphy, which provides a measure of lymphatic function, has been studied in patients with chronic venous leg ulceration and compared with healthy controls.[12] This study showed a significant decrease in lymphatic function in ulcerated and nonulcerated limbs of patients under 65 years old compared with healthy control limbs. The study also demonstrated a significant reduction in lymphatic function with age. This may explain the increased morbidity from venous ulceration in elderly patients.

Morphological studies on skin biopsies taken from patients with CVI demonstrate structural changes in dermal lymphatic vessels. There is collapse of lumina of intradermal lymphatics, loss of the open intercellular junctions, and damage to the anchoring filaments which maintain the lymphatic vessel open.[13] As described above, these features lead to the loss of the normal one-way transport mechanism of the initial lymphatics and consequent impairment of lymphatic function. In severe CVI, lipodermatosclerosis may occur with ulceration. A morphological study in lipodermatosclerosis has shown a complete absence of lymphatics in the ulcer bed and a marked decrease in the number of lymphatics surrounding the ulcer. In association, there was destruction of the endothelium and muscle lining of lymphatics present.[14]

Therefore, there is clinical and laboratory evidence that with the pathological changes in blood vessels due to CVI, there is concomitant pathology in lymphatics which lead to a deterioration in lymphatic function.

In addition, lymphatic function may be compromised due to congenital or acquired factors. A primary reduction in the number of lymphatics, similar to an elderly patient, may compromise lymphatic function and allow edema to appear more quickly in CVI. Operative procedures, for example varicose vein stripping, may also lead to lymphatic obliteration and functional compromise. Cellulitis, which may cause lymphangitis, can similarly disrupt lymphatics, probably by lymphatic vessel occlusion. Any process leading to lymphatic dilatation or luminal destruction can create lymphatic valvular insufficiency and lymph reflux, analogous to the loss of venous valve function in CVI. The intrinsic contractility of lymphatics is vital to lymph flow, particularly with lower limb immobility and loss of this contractile mechanism is likely to play a major role in lymphatic failure and tissue edema.[15]

In summary, a number of associated factors may occur together with the pathological lymphatic changes associated with CVI to explain the common occurence of edema in CVI.

THE IMPLICATIONS OF LYMPHATIC DYSFUNCTION

The presence of edema complicates the management of CVI and particularly venous ulceration. Edematous tissue will lead to increased exudation from wounds which will macerate and damage the skin surrounding ulcers, impairing wound healing. The presence of edema is associated with longer duration of ulcer.[9] Dressings will need to be

changed more often, necessitating an increase in resources.

Moist dressings and macerated tissue are also an ideal environment for proliferation of microbes, which may lead to infection and the concomitant inhibition of wound healing. The inflammation in association with infection will increase capillary permeability and produce tissue factors, which further increase the load on the lymphatics, setting up a vicious circle.

In the setting of chronic edema, hyperkeratosis, papillomatosis, and eventually fibrosis (elephantiasis) occur. This increases the debris from the legs and creates an increased surface area with sanctuary sites for microbes, further increasing the risk of superinfection.

The lymphatic dysfunction means a loss of the immune surveillance role in the affected limb. This sets up a localized immunodeficiency and is the likely reason for an increase in cellulitis in patients with lymphedema but not venous disease. As described, cellulitis can lead to lymphatic destruction, and further compromise lymphatic function.

Squamous cell carcinoma (SCC) is a recognized complication of chronic venous ulceration, although it is unclear whether this is due to chronic ulceration or lymphatic insufficiency. SCC occurs in the setting of generalized immunodeficiency, for example organ transplant recipients, and once again lymphatic dysfunction and concomitant immunocompromise may be implicated.

The practical result of an increase in tissue fluid in the lower limbs of patients with CVI is "heavy legs" leading to a loss of mobility and increased likelihood of leaving the lower limbs dependent. The consequent decreased venous return and worsening of tissue edema will further perpetuate the problem.

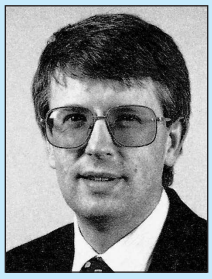
The principles of treatment of venous disease and lymphatic dysfunction are therefore very similar. The importance of the calf pump is well recognized in improving venous return, and this will also have an impact on relieving edema. Elevation will similarly make an impact on both problems, and is vital during rest or in the setting of lower-limb muscle paralysis.

Compression therapy in the form of four-layer bandaging is the same in principle as multilayer bandaging for lymphedema. The resultant increase in venous return and increase in stiffness of the tissues will decrease edema formation and improve lymphatic function. Once bandaging has had the desired effect, prophylactic compression hosiery will perform the same function.

The skin changes of severe CVI and the resultant chronic edema need to be avoided. Whilst attending to the primary pathology, it is important to use adequate emollients to maintain skin hydration, topical corticosteroids if required for eczematous changes, and possibly keratolytic agents for troublesome hyperkeratosis.

In the future, surgery may have a role to play particularly in the treatment of the postthrombotic limb. However, it is vital that no further damage is inflicted on lymphatics during surgical procedures.[16]

The ideal medical treatment for CVI would achieve both a decrease in capillary filtration and an improvement in lymphatic function. There is clinical and laboratory evidence that Daflon, a micronized purified flavonoid fraction, has these properties and is a useful adjunctive treatment in severe CVI.[17]



Address for correspondence
Peter S. MORTIMER
St George's Hospital Medical School, London SW17 0QT
e-mail:p.mortimer@sghms.ac.uk

Address for correspondence
Ian C. PEARSON
St George's Hospital Medical School, London SW17 0QT
e-mail: ianpearson@doctors.org.uk

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1st Latin American Consensus on the management of lymphedema

José L. CIUCCI
and the Consensus Group*

Central Military Hospital,
Buenos Aires, Argentina

SUMMARY

From 21 to 23 March 2003, the First Latin American Consensus Conference on the management of lymphedema was held in Buenos Aires, Argentina. The panel was composed of distinguished Latin American experts* in the area of lymphology, who discussed the following topics: definition and classification of lymphedema; diagnostic methods including lymphoscintigraphy, colour Doppler ultrasonography, direct or contrast capillaroscopy, and magnetic resonance imaging. Treatments: manual lymphatic drainage, sequential pneumatic compression, elastic compression, and benzopyrones. Multidisciplinary management: the nervous system and lymphedema, lymphedema and pain, the musculoskeletal system and lymphedema, cutaneous manifestations associated with lymphedema, lymph flow-enhancing exercises, nutrition and lymphedema, psychotherapy,and preventive recommendations. Lymphangitis: erysipelatoid lymphangitis, prophylactic treatment of lymphangitis, and immunotherapy in the treatment of lymphangitis. Surgical treatment: indications and advances in the surgical treatment of lymphedema, lymphatic-vein anastomosis with zero venous pressure, resection procedures, complications of surgery and their treatment, and informed consent.

INTRODUCTION

The desirability of a consensus conference on lymphedema had long been recognized when the Argentinian School of Lymphology was finally able to bring this project to fruition. From March 21 to 23, 2003, the First Latin American Consensus Conference on the management of lymphedema was held, in the province of Buenos Aires, Argentina. With the participation of distinguished lymphologists from across Latin America, the conference reviewed topics ranging from the classification of lymphedema to various aspects of the diagnosis and treatment. The conference proceedings will be reported in a special publication within the course of the year. The importance of this event stems, among other things, from the fact that for the first time the most renowned experts from Latin America were brought together to express their opinions, describe their practice, and present their ideas, the ultimate goal being to allow patients with

lymphedema to achieve reintegration within their communities. Experts from many countries on our continent honored us with their presence, representing Brazil, Colombia, Cuba, Ecuador, Mexico, Uruguay, Venezuela, and various provinces of Argentina.

DEFINITION AND CLASSIFICATION OF LYMPHEDEMA

The definition of lymphedema was discussed and determined by consensus among the panel members as follows: lymphedema is an accumulation of water, salt, electrolytes, high-molecular-weight proteins, and other compounds within the interstitial compartment as a result of a dynamic or mechanical disturbance in the lymphatic system, the consequence being gradual and progressive enlargement of the affected extremity or other region of the body, accompanied with declines in functional and immunological capabilities, increased weight, and morphological changes.

A staging and classification scheme for lymphedema was developed on the basis of correlations linking pathophysiology, imaging study findings, and the morphology of the affected extremities. Using these correlations, various stages were defined for the classification of lymphedema. This classification system will serve as a tool for drawing a detailed picture of the condition, its natural history, and its course, while at the same time allowing physicians to determine the stage in each individual patient and, therefore, to select the appropriate treatment.

DIAGNOSTIC METHODS

The importance of lymphoscintigraphy in the diagnosis of lymphedema was discussed. This minimally invasive method has replaced, in some cases, contrast lymphography and can detect functional changes in the lymphatic system. The main advantage of lymphoscintigraphy is its ability to visualize the lymphatic flow without requiring catheterization of a lymphatic vessel, thereby eliminating the risk of injury to the lymphatic system. Although the anatomic resolution is low, new radiopharmaceuticals provide excellent contrast between the lymphatic system and the surrounding tissues. This reproducible diagnostic investigation carries no risk of allergic reactions or adverse effects. Lymphoscintigraphy is ascending and indirect; it provides information on both the transport function of the lymphatics (dynamic lymphography) and the function of lymph nodes (static lymphography). Acquisition can be static, dynamic, or by whole body scanning. The lymphatic system can be stimulated by active or passive mobilization of the limb under investigation. Examination of both sides for comparative purposes and comparison of images before and after treatment are recommended.

The role for ultrasonography and Doppler studies in the diagnosis of edema and lymphedema was discussed. When evaluating edema of the extremities, color ultrasonography is particularly useful, as it is both cost-effective and noninvasive. However, this technique provides only limited information on the anatomy and physiology of the lymphatic system and may be viewed as an ancillary method for the differential diagnosis of edema of the extremities and, in some specific cases, of lymphedema. The diagnosis of lymphedema is one of exclusion: other causes of edema of the extremities must be ruled out. The clinical picture and a number of ultrasonography findings assist in the diagnosis. *Lymph nodes may be visible when they are hypertrophic. *Obstructive lymphedema: matted metastatic nodes characterized by increased cortical echogenicity and unevenness of the capsule contours. With venous Doppler, compression may result in absence of color and loss of the spontaneous phasic flow. In primary lymphedema, distal ectasia of the vessels is visible, as well as absence of collecting lymphatics.

The panel agreed that capillaroscopy, whether direct or with fluorescein as a contrast agent, is not reliable for evaluating the lymphatic capillaries. Fluorescent agents such as Dextran 150 000 labeled with fl Na must be used to assess the lymphatic capillary networks, collecting ducts, and precollecting ducts. The fluorescent agent is injected under the dermis. Microscopic examination using a contrast capillaroscope can show normal images, with intact networks seen as ring-shaped spots and subepidermal spots. Abnormal aspects include blockage of the contrast agent, absence of spot development, dilation or unevenness of the rings, and leakage of the contrast agent through breached capillaries. One of the most important contributions of capillaroscopy to the diagnosis of lymphedema is dermal backflow after injection of the contrast agent. This has not been observed in normal patients. Today, microlymphography is extremely useful both for establishing the diagnosis and for classifying lymphedema.

Magnetic resonance imaging (MRI) is a noninvasive diagnostic method that is sensitive for differentiating lymphedema from other types of edema. In a few cases, MRI can indicate the cause of the lymphedema.

TREATMENT

Manual lymphatic drainage

Manual lymphatic drainage (MLD) is a treatment modality involving gentle maneuvers with pressures that do not exceed 40 mm Hg. MLD promotes the penetration of high-molecular-weight proteins into the initial lymphatic capillary and simultaneously stimulates contraction of the lymphatic vessel, thereby increasing the flow of lymph through the subdermal plexus and through the collaterals of the affected limbs. The patient is recumbent and the skin uncovered, with no substances interposed between the hands of the therapist and the patient. The manoeuvers performed during MLD follow the direction of the lymph flow. The rhythm should be slow, about 10 to 12 per minute. The duration of each session varies from 15 to 50 minutes.

Contraindications include acute infections, superficial and deep venous thrombosis, active neoplastic disease, and decompensated systemic conditions.

Sequential pneumatic compression

Sequential pneumatic compression is among the components of the conservative treatment of lymphedema. Current data indicate that 90% of cases of lymphedema respond favorably to conservative treatment. Sequential intermittent pneumatic compression (SIPC) should always be performed after a session of MLD. It increases the interstitial pressure, thereby promoting drainage of the fluid trapped in the interstitial compartment and promoting reduction of the edema. SIPC relies on pneumatic pumps comprising multiple chambers, which fill and empty independently from one another. The chambers work intermittently and sequentially in the distal-to-proximal direction.

The latest-generation pumps have 10 to 12 overlapping chambers designed to fragment the sequential pressures.

The pressure applied to the limb varies from 20 to 40 mm Hg in order to avoid injury to the lymphatic system; each session may last from 30 minutes to several hours. Before applying the pump, MLD must be performed to relieve obstruction in the body sectors proximal to the site of action of the pump. SIPC is contraindicated in patients with active erysipeloid lymphangitis, thrombophlebitis, heart failure, pulmonary edema, or venous thrombosis.

Compression with elastic bandages

Elastic bandage compression is at the core of every treatment program for lymphedema of the limbs. This modality should be used during the first treatment phase. Multilayered bandages ensure a high level of compression by combining a passive-protective layer and several active layers of very low-or low-stretch bandages, applied in a superimposed or overlapping arrangement, with sufficient tension to fit snugly around the limb. These bandages have a low resting pressure, of 10 mm Hg, contrasting with a high working pressure ranging from 25 to 50 mm Hg. Their effects are ascribable to reabsorption of protein and water; they increase the effectiveness of the soleus-gastrocnemius pump and protect the diseased limb. Contraindications include local infection, significant arterial disease, and in situ neoplastic lesions. The orthopedic industry has developed a series of graduated elastic compression garments; thus, for upper-limb lymphedema, elastic sleeves with or without gloves are available, whereas for the lower limbs hosiery reaching up to the knee, thigh, or waist can be used. These garments apply graduated compression that decreases from the distal to the proximal limb, usually from 20 to 40 mm Hg, and exhibit medium to high elasticity. These orthopedic devices should be made of hypoallergenic material, easy to put on and take off, well tolerated, and durable. Elastic garments are indicated when the patient moves from the induction or aggressive treatment phase to the maintenance phase of physical therapy. Given the high resting pressure, they should be put on when the patient awakens in the morning and kept on until bedtime or until signs of intolerance develop.

Pharmacotherapy

It has been demonstrated that benzopyrones act via several distinct mechanisms and are extremely effective in the treatment of edema characterized by a high concentration of proteins, in particular primary and secondary lymphedema. The most widely used are the gamma benzopyrones, and among these micronized diosmin/hesperidin, which is indicated at individually tailored dosages. The dosage should be titrated, starting with 1500 mg and increasing the amount each week, to no more than 3000 mg. These agents are extremely effective and have few side effects. In follow-up studies, no evidence of nephrotoxicity or hepatotoxicity developed, even with prolonged treatment at effective therapeutic dosages.

MULTIDISCIPLINARY TREATMENT

Dr José Luis Ciucci presented an introduction on the multidisciplinary treatment of lymphedema, pointing out that close collaboration among team members working in a single facility plays a key role in reintegrating lymphedema patients in the community. The composition of the team, as well as the role of each team member, was discussed.

A number of disease states, including lymphedema, affect the nervous system. The clinical presentation is variable; stretching of the nerves manifests mainly as motor deficits followed by sensory disturbances, whereas compression predominantly induces sensory deficits. A less common presentation is hypoesthesia/dysesthesia without motor loss after radiation therapy to the axillary region. A variety of diagnostic investigations should be used to determine the severity of the nerve damage. The treatment varies according to the severity and nature of the nerve lesions; the diagnosis should be established as early as possible to ensure optimal treatment results.

Lymphedema and pain

Another topic discussed at the conference was lymphedema and pain. Special attention was directed to pain caused by lymphedema after treatment for breast cancer. The pain may be somatic or neuropathic. The first-line treatment of somatic pain is nonsteroidal anti-inflammatory drug (NSAID) therapy, with or without adjuvant medications. Weak opiates are used as second-line therapy; when this fails, strong opiates are given in combination with NSAID therapy, with or without adjuvant medications. Neuropathic pain requires treatment with adjuvant analgesic agents such as anticonvulsant medications, antidepressants, topical anesthetics, etc, either alone or in combination with other analgesics. It is worth pointing out that psychotherapeutic support should be provided concomitantly.

Functional impairment

The presentation on the musculoskeletal system and lymphedema highlighted the problems raised by functional impairment in limbs affected with lymphedema. Alterations in the epifascial structures are the main cause of functional impairment, rather than alterations in the subfascial structures. Computed tomography (CT) and MRI studies of the extremities have shown changes in the cellular subcutaneous tissue caused by fluid accumulation or fibrosis, with the characteristic honeycomb appearance and skin thickening and fibrosis; the bone and muscle structures, in contrast, remain normal.

Cutaneous manifestations and postmastectomy lymphedema

The cutaneous manifestations associated with postmastectomy lymphedema were discussed. The clinical manifestations depend on the number of lymph nodes removed and on the effects of radiation therapy. The nails, as well as the hair, are highly sensitive to various stimuli. These insults can produce an abrupt arrest in nail and hair growth. Thus, in patients with lymphedema, the nails may become yellow, opaque, and dystrophic. *Infectious skin diseases: lymphangitis, erysipelas, interdigital mycotic infections. *Traumatic lesions: excoriations, manicure-induced lesions. *Paraneoplastic skin diseases: malignant neoplasms may be associated with dermatological lesions that have no malignant characteristics per se but are directly related to the presence of the tumor. Thus, their course runs parallel to that of the malignancy: they resolve after surgical removal of the tumor and recur if the tumor recurs. Examples include paraneoplastic acrokeratosis (Bazex syndrome), erythema gyratum repens, acquired acanthosis nigricans, and paraneoplastic pemphigus (Cowden syndrome). *Skin metastases: a variety of clinical patterns exist. Carapace cancer: tumor spread to the subepidermal lymphatic spaces leads to the development of nodules in an erythematous-edematous area, usually located over the anterior chest wall in patients with breast cancer. Malignant erythema (Hutchinson syndrome) related to tumor cell spread via the deep dermal veins. Telengiectatic carcinoma produced by dissemination of tumour cells through small and superficial vessels. Stewart Treves syndrome (lymphangiosarcoma), in which nodular metastases develop on slightly erythematous and painful skin.

Lymph flow-enhancing exercises rely on muscle contractions to improve the flow of lymph; they constitute a training program that provides the patient with the gains needed to achieve reintegration into the community. When designing a training program, the location of the lymphedema and the extent of damage to muscle masses or nerves should be taken into consideration. All exercises that cause pain should be eliminated: thus, pain serves as a limiting signal. Exercises requiring maximum force should also be avoided. The focus should be on improving flexibility of the muscles and dermis, in order to optimize drainage through the veins and lymphatics. Integrated activity is of the utmost importance and should always be conducted under continuous medical supervision.

Nutrition and lymphedema

Links between nutrition and lymphedema were discussed. Lymphedema influences the nutritional status via a number of mechanisms. The chronic nature of lymphedema induces an emotional imbalance that modifies the patient's quantitative and qualitative choice of foods, thereby directly influencing the nutritional status, causing either overnutrition or undernutrition. These nutritional disorders alter the immune responses, increase the existing edema by inducing hypoproteinemia, induce further trophic abnormalities in the skin and appendages, and hamper the healing of wounds, should any occur. Failure to recover a satisfactory nutritional balance leads to increased emotional distress, generating a vicious circle that can have devastating effects. Conversely, a satisfactory nutritional status increases the chances of a favorable outcome and diminishes the risk of intercurrent diseases.

For each individual patient, a nutritional program should be designed according to the underlying comorbidities and to their negative effects. To this end, after an evaluation of the patient's nutritional status, the indications for nutritional therapy should be determined. Immune status improvement should be achieved by supplementation with arginine, glutamine, omega n-3 fatty acids, and antioxidants, as the underlying diseases in these patients generate an increased susceptibility to infections. Lymphedema may be associated with nutritional disorders such as overweight, obesity, dyslipidemia, protein-calorie malnutrition, and anemia; thus, special care should be taken when determining the appropriate nutritional program to ensure that there will be no negative impact on concomitant diseases.

Psychotherapy in lymphedema

Psychotherapy was incorporated into treatment programs for lymphedema when lymphedema specialists became aware of a need among their patients to discuss topics that fell outside the province of lymphology and phlebology but were within the realm of ethical and humanistic concerns shared by all physicians. Psychotherapy provides the patient with an opportunity to express unmet needs, pain, anxiety, etc. In addition, psychotherapists develop a close relationship with the patients in order to determine the meaning of the disease, which is not immediately obvious. The psychotherapist attempts to give this meaning a place in the life history of the patient, going beyond the effect of the condition on the body. Psychotherapists collaborate directly with the patient, striving to work through the psychological aspects present in the cause of the disease and evident in the physical deformity produced by the lymphedema. They work in collaboration with the other members of the management team in an effort to broaden the vision of the healthcare professionals involved in treating the patient, by integrating the role of psychological factors into the explanation of the symptom and its time course, as well as by analyzing distubances in the patient-physician or patient-health care team relationships.

The family members are also included, most notably when the patient is a child. Taking these aspects into account facilitates the work of all the team members. By offering the patients an opportunity to speak about their experience at the same time as they receive medical and surgical treatment, medications, physiotherapy, and nutritional therapy, psychotherapy maximizes the efficacy of each of these components of the management program.

Preventive measures for patients with lymphatic system disorders: patients with latent or clinically patent lymphedema, as well as their family, must receive information on the importance of preventing further damage to their lymphatic system, which might promote the development of lymphedema or worsen existing lymphedema. Effective prevention involves maintaining the trophism and humidity of the skin and appendages; avoiding injuries, such as cuts or contact with skin irritants that might cause contact dermatitis; early treatment of skin lesions such as eczema, folliculitis, or mycotic infections; elimination of intradermal, subcutaneous, and intramuscular injections; avoiding burns related to hot water or exposure to sunlight; and avoidance of muscular effort, carrying heavy loads, and wearing tight garments.

LYMPHANGITIS

The panel considered a protocol for the treatment of erysipelatoid lymphangitis designed to optimize outcomes while shortening hospital stay times and expediting the return to work. The initial induction phase involves antibiotic therapy, anti-inflammatory agents, analgesics, micronized diosmin/hesperidin, and lymphokinetic agents, selected based on the severity of the condition. Once the infectious process is under control, the second phase consists in initiation of multidisciplinary treatment combining drainage, pump therapy, lymph flow-enhancing exercises, skin care, etc, in conjunction with psychotherapy. Finally, the third phase consists of supportive therapy

in those patients whose lymphedema fails to respond satisfactorily to the previous treatments. The drainage and pump therapy are continued, and specialists ensure direct control of comorbidities.

Another focus of discussion was the prophylactic treatment of lymphangitis: a number of prophylactic measures should be recommended in every patient, including proper hygiene and nutrition and avoidance of contact with pointed or cutting instruments. An additional measure is administration of a vaccine consisting of a suspension of dead cells, called Inmunoparvum, manufactured by the pharmaceutical company of Pernambuco state (LAFEPE). This vaccine has produced good results.

Another topic discussed at the conference was immunotherapy in the treatment of lymphedema. The panel examined the results of sublingual or subcutaneous immunotherapy in the prevention of recurrent lymphangitis. A comparison of the sublingual and subcutaneous vaccines showed that the sublingual route had no disadvantages as compared to the subcutaneous route. Sublingual immunotherapy with bacterial extracts (streptococci and staphylococci) was deemed a valid alternative in the treatment of recurrent lymphangitis. Results in the patients proved very good, as 80% had good outcomes and 20% fair outcomes. The antistreptolysin O test detected the production of antibacterial antibodies that may be stimulated by the vaccine. Although no relation has been found between antistreptolysin O test results and outcomes, the results after 3 years of treatment indicate that vaccination may have ensured the development of defense mechanisms against these organisms, which are susceptible to the effects of antibodies.

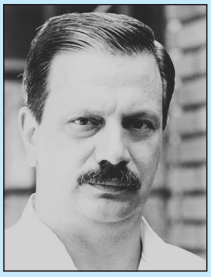
SURGICAL TREATMENT

The indications and limitations of surgical treatment for lymphedema were discussed. A surgical procedure performed *appropriately* optimizes the benefits produced by medical and physiotherapeutic means or allows these means to become effective by restoring drainage of the lymph through anatomically and physiologically intact lymphatic vessels; in this situation, lymphatic-venous anastomoses may be beneficial. In patients with chronic lymphedema, the goal is initial or residual reduction of the existing "lymphedema mass" or resection of the irreducible collagen mass (which may promote recurrences of infectious episodes), thereby improving the course of the disease.

A technical innovation in the area of lymphatic venous anastomoses was presented, namely, lymphatic-venous anastomosis with zero venous pressure in patients with lower limb lymphedema and an intact greater saphenous vein. The greater saphenous vein, whose ostial valve is competent, is converted to a cavity with no venous flow via ligation of the opening of the anastomosis and section of all the collaterals; this creates a substitute for the thoracic canal. The lymphatic-venous anastomoses are then performed with this nonfunctional venous segment.

The panel agreed that the resection surgical procedures used today in the management of lymphedema include: dermolipectomy, which consists merely in focal excision of the excess skin and subcutaneous cellular tissue followed by edge-to-edge suture and closed suction drainage. Liposuction: used mainly in postmastectomy lymphedema. Penoscrotal reconstructive surgery: using the Cordeiro technique. If the lymphedema is secondary to chylous reflux due to incompetence of the valves in the ileolumbar lymphatic vessels, the ileolumbar lymphatic chains should be ligated before the penoscrotal reconstructive procedure. Amputation is used in patients with malignant lymphedema and extensive lymph node destruction. A number of complications can occur. *After bypass surgical procedures:* damage to afferent lymphatic vessels, development of clots, suture dehiscence, absence or loss of union among endothelia, surgical infection, lymphocele, loss of contractility of the lymphatic vessel, and fibrotic changes in the distal lymphatics and in the lymph nodes. *After surgical resection procedures:* hemorrhage, surgical wound infection, skin necrosis, nerve lesions, venous thrombosis, and lymphorrhea. *After surgery for penoscrotal lymphedema:* infection, tissue necrosis, nerve lesions, abnormal scar formation, skin implant rejection, and impotence. Given the huge risk of complications, caution is required, and care should be taken to select the appropriate treatment; should complications occur, they must be treated as promptly as possible.

The physician should always be the coauthor of the informed consent document signed with the patient, failing which the physician is vulnerable to malpractice litigation. Consequently, the vital importance of this document as a medical act should be borne in mind, as well as the specific limitations and circumstances that make this act complex and difficult.



Address for correspondence

Prof José Luis Ciucci, MD, PhD

Head of Department of Phlebology and Lymphology, Central Military Hospital, Buenos Aires, Argentina

Monte de Oca 789
1er Piso
1270 Buenos Aires
Argentina

Tel: + 54 (11) 43 03 28 29
e-mail: joseciucci@hotmail.com.ar
jciucci@intraned.net.ar

FURTHER READING

Ciucci JL. Linfología. 1st Latin American Consensus on the management of lymphedema. Buenos Aires: Escuela Argentina de Linfología;2003.

* Consensus delegate members

Dr Solange Do Camo Neto Gomes
Dr Delia Ela Charles Edoward Otrante
Dr. Delia Esther Mena FLor
Dr Henrique Jorge Guedes Neto
Dr Alejandro Latorre Parra
Dr Salvador Nieto
Dr María Esther Mancebo Vas
Dr Cleusa Ema Quilici Belczak
Dr Osvaldo Curto
Dr Mauro Andrade
Dr Raúl Ángel Beltramino
Dr Luis Rossi
Dr Ángel Esteban Guzmán
Dr Luis Felipe Gomez Isaza
Dr Mario Bravo
Dr Elena Ana Schrott de Videla
Dr Julio Alfonso Ayguavella
Dr Jorge Enrique Soracco
Dr Juan Carlos Krapp
Dr Eugenio Oscar Brizzio
Dr Luis Fernando Flota Cervera
Dr Luis Daniel Marcovecchio
Dr Anacleto Carvalho

* Guest experts

Dr Héctor Caldevilla
Dr Gonzalo Javier Bonilla
Dr Ana Cristina Zarlenga
Dr Beatriz Afonso
Prof María Alesandra Pancheri
Dr José Luis Covelli
Dr Raúl Antonio Zócoli
Dr Claudia Simeone
Lic Mirta Critelli de Isola
Lic Inés Lamuedra

Congress and conference calendar

ANGIOLOGICAL DAYS 2004

This congress will be held in Prague (Czech Republic) from February 19 to 21, 2004.

• *For further information, please contact:*

President: Karel Roztocil
Masarykova kolej
Thákurova 1
160 41 Prague 6, Czech Republic

Tel: + 420 233 051 226
Fax: + 420 233 051 155

e-mail: uhrova@suz.cvut.cz
congress@suz.cvut.cz
karel.roztocil@medicon.cz
Website: www.angiologie.cz

VIth ANNUAL MEETING OF THE AUSTRIAN SOCIETY FOR WOUND HEALING (AWA)

This congress will be held in Graz (Austria) from February 27 to 28, 2004.

• *For further information, please contact:*

AWA Sekretariat
Postfach 65
1095 Vienna, Austria

Tel: + 43 1 879 03 79
Fax: + 43 1 879 04 90
e-mail: office@a-w-a.at

ANNUAL MEETING OF THE AUSTRIAN SOCIETY FOR PHLEBOLOGY

This congress will be held in Oberlech am Arlberg (Austria) from March 13 to 20, 2004.

• *For further information, please contact:*

President: Prof Dr W. Jurecka

MFC – Masi Fuchs Congress
Postfach 6
1106, Vienna, Austria

Tel: + 43 1 602 25 48
Fax: + 43 1 602 25 48
e-mail: congress@telering.at

VIIIth INTERNATIONAL MEETING OF COLOPROCTOLOGY

This congress will be held in Saint Vincent (Italy) from March 29 to April 1, 2004.

• *For further information, please contact:*

President: Dr Ezio Ganio

Tel: + 39 0125 612 400
Fax: + 39 0125 414 567
e-mail: ganio.ezioponet.it

IInd EADV INTERNATIONAL SPRING SYMPOSIUM

This congress will be held in Budapest (Hungary) from April 29 to May 1st, 2004.

• *For further information, please contact:*

President: Attila Horvath

MOTESZ (Congress and Travel Agency)
Nádor u.36.
H-1051 Budapest, Hungary

Tel: + 39 1 311 66 87
Fax: + 39 1 383 79 18

e-mail: eadvbudapest@motesz.hu
congress@motesz.hu
Website: www.eadvbudapest2004.com

XXIst WORLD CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY

This congress will be held in Rome (Italy) from May 22 to 26, 2004.

• *For further information, please contact:*

President: Prof S. Novo

Via Sardegna, 76
90144 Palermo, Italy

Tel: + 39 91 511 375
Fax: + 39 91 526269

e-mail: novosav@unipa.it

VIIIth ANGIOLOGICAL SYMPOSIUM

This congress will be held held in (Ostrava) from June 16 to 18, 2004.

• *For further information, please contact:*

CVUT - SÚZ Kongresové oddelení

Masarykova kolej
Thákurova 1
160 41 Prague 6, Czech Republic

Tel: + 420 233 051 226
Fax: + 420 233 051 155

e-mail: uhrova@suz.cvut.cz

congress@suz.cvut.cz
Website: www. angiologie.cz

Karel Roztocil, M.D.

IKEM

Department of peripheral circulation
Vídenská 1958
140 21 Prague, Czech Republic

e-mail: karel.roztocil@medicon.cz

Vth MEETING OF EUROPEAN VENOUS FORUM

This congress will be held in Warsaw (Poland) from June 25 to 27, 2004.

• *For further information, please contact:*

President: Prof Arcadiusz Jawień

Katedra I Klinika
hirurgii Ogólnej
Ul. Ujejskiego 75
85-168 Bydgoszcz, Poland

e-mail: ajawien@ceti.com.pl

XIIth UNITED EUROPEAN GASTROENTEROLOGY FEDERATION (UEGF)

This congress will be held in Madrid (Spain) from Septembre 25 to 30, 2004

INTERNATIONAL UNION OF PHLEBOLOGY (UIP) XVth WORLD CONGRESS

This congress will be held in Brazil (Rio de Janeiro) from October 2nd to 7th, 2005.

• *For further information, please contact:*

President: Angelo Scuderi, MD

Universita di Ferrara – Chirurgia Vascolare
Rio UIP 2005
Rue Sancta Clara, 494
Sorocaba - SP - 18035 - 421
Brazil

Tel: + 55 15 231 6619
Fax: + 55 15 221 4074

e-mail: inspemoc@dglnet.com.br
angelo.scuderi@flebologiabrasil.com.br

Website: www. flebologiabrasil.com.br

LYMPHO 2004

This congress will be held in Brno (Czech Republic) from October 8 to 9, 2004.

• *For further information, please contact:*

President: Prof Oldrich Eliska

CVUT - SÚZ Kongresové oddelení

Masarykova kolej
Thákurova 1
160 41 Prague 6, Czech Republic

Tel: + 420 233 051 226
Fax: + 420 233 051 155

e-mail: uhrova@suz.cvut.cz
congress@suz.cvut.cz
www.mujweb.cz/www/lympho

XXIXth PHLEBOLOGICAL DAYS

This congress will be held in Hradec Králové (Czech Republic) from October 21 to 22, 2004.

• *For further information, please contact:*

Congress Business Travel, s.r.o.

Lidická 43/66
150 00 Prague 5, Czech Republic

Tel: + 420 224 942 575-9
Fax: + 420 224 942 550
e-mail: senderova@cbttravel.cz

President: Jaroslav Strejcek, M.D.

Centrum dermatologické angiologie
Na Konvárce 6
160 00 Prague 6, Czech Republic
e-mail: strejcek@ri.ipex.cz

EUROPEAN SOCIETY OF SURGERY – VIIIth ANNUAL MEETING

This congress will be held in St Julian's (Malta) in November 2004

• *For further information, please contact:*

President: Prof L. Cutajar

Chairman, Organising Committee, ESS Meeting
Department of Surgery, The Medical School
G'Mangia, Malta

XXVIth CONGRESO NAZIONALE DELLA SOCIETA ITALIANA DI ANGIOLOGIA E PATOLOGIA VASCOLARE (SIAPAV)

This congress will be held in Messina - *to be confirmed* - (Italy) in November 2004.

• *For further information, please contact:*

G.C. Congressi

Via P.Borsieri n.12 - 00195 - Roma, Italy

President: Claudio Allegra, N. Longo

C. Allegra: Osp. S.Giovanni Serv. Angiologia
Via S.Giovanni in Laterano n.155 - Roma, Italy

Tel. + 39 06/77.055.243
Tel: + 39 06/37.00.541
Fax: + 39 06/37.35.23.37

e-mail: md2535@mclink.it

XVth WORLD CONGRESS OF THE UNION INTERNATIONALE DE PHLEBOLOGIE

This congress will be held in Rio de Janeiro (Brazil) from October 2nd to 7th, 2005.

• *For further information, please contact:*

Chairman: Angelo Scuderi

RIO UIP 2005 Secretary
Rua Santa Clara, 494
Sorocaba
18030-421- SP, Brazil

Tel: + 55 15 231 6619
Fax: + 55 15 221 4074 / 232 9241

e-mail: inspecmoc@dglnet.com.br
angelo.scuderilebologiabrasil.com.br
Website: www.flebologiabrasil.com.br

SERVIER RESEARCH FELLOWSHIP

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Submission deadline:
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The competition is open to young candidates who have a specific interest in the field of phlebolymphology and are a member of a national society in this field. The projects must consist of **original clinical or basic research** in an area of phlebolymphology, such as anatomy, physiology, patho-physiology, diagnostic methods, or clinical research. The fellowship will be made available from 1 November 2005 and end in October 2007.

The review of the submitted projects and the selection of the best candidate will be made by a committee of **recognized worldwide specialists** in the field of phlebolymphology.

Send us your project at the following address:

Jean-Jérôme GUEX
Fonds de Recherche de l'UIP
32, boulevard Dubouchage
06000 Nice, France

Next winner awarded at the UIP World Congress in Rio de Janeiro (October 2005)

The last research fellowship winner, Dr Maria Gemma PASCUAL GONZALEZ (Vascular Biology, Spain) was awarded the grant at the 2003 UIP Chapter in San Diego for her project "Elastin dysregulation in varicose veins".

Invitation to the 2007 UIP Chapter to present the project's results

Candidates must submit a synopsis of 8 to 10 pages, double-spaced, typewritten in English, in the form of 5 original printed copies. The synopsis should clearly present the objectives, methodology, planning, and references of the projected work. Candidates must also submit a curriculum vitae and a letter from a referee supporting the project and confirming its backup, together with details of how the fellowship money will be spent. After the first year of work, the award-winner must submit to the committee a synopsis of progress so far. The project's results will have to appear in a form suitable for publication in an international journal.

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