VL-DUAL SHORT REVIEW

Revisit to Phlebolymphedema as Ultimate Outcome of Dual Outflow System Failure

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Abstract Venous and lymphatic systems are one interdependent, 'inseparable' dual-outflow system of the circulation. Both systems are 'mutually complimentary'; the insufficiency or overload to one of two systems allows the other to play an auxiliary role of fluid return through micro- & macro-anastomosis. But both systems are 'mutually complimentary' only when they are with normal function; when the venous stasis exceeds this maximum lymphatic compensatory capacity, the insufficiency becomes 'phlebo-lymphatic'. When one of the two systems should fail to provide sufficient compensation to the other system, it would become a combined condition of chronic venous insufficiency (CVI)/chronic venous hypertension and chronic lymphatic insufficiency (CLI)/chronic lymphedema, known as "phlebo-lymphedema" (PLE). Hence, the ulcer of PLE origin represents an unavoidable outcome of the joint failure of this "inseparable" venous-lymphatic circulation system, presenting as a combined condition of veno-lymphatic edema caused by CVI and CLI. When the lymphatic system becomes damaged (mechanical insufficiency) or the ultrafiltrate load becomes greater than the ability of the lymphatic system to drain it (dynamic insufficiency), the lymphatic system would fail to handle the interstitial fluid load, and the proteins and macromolecules start to accumulate in the interstitium. This 'presence of proteins in the interstitial space' further induces an inflammatory cascade to create a proinflammatory state leading to the irreversible changes. These proteins may serve further as a substrate for microorganisms to facilitate extending and intensifying infections. Increased scarring and trauma by these infections cause further damage to the vulnerable lymphatic collectors. Therefore, lymphatic system can be easily damaged not only by drainage overload but also by the inflammatory environment created by the fluid stasis so that this vicious circle created by the impairment of the venous and lymphatic system would cause the ulcer management more seriously complicating. Hence, a precise understanding of the nature of all the chronic 'indolent' venous stasis ulcers as a combined condition of veno-lymphatic edema caused by CVI and CLI of various origins is mandated based on simultaneous evaluation of these two closely linked conditions/systems.

Keywords dual-outflow system; mutually complimentary; chronic venous insufficiency (CVI); chronic lymphatic insufficiency (CLI); phlebo-lymphedema" (PLE); venous stasis ulcers

General overview

'Phlebolymphedema' has been well recognized through decades as a unique hemodynamic condition to represent a combined condition of chronic venous insufficiency and chronic lymphatic insufficiency as the ultimate outcome of simultaneous failure of venous-lymphatic system[1-4].

Indeed, the venous and lymphatic systems function together as closely linked 'dual outflow' system although both systems functions based on two entirely different fluid-dynamic principles. Normal lymphodynamic is based on self-propelled peristalsis by each unit of 'lymphangion' with positive pressure of 50-60mmHg while venodynamics is purely based on a passive low-pressure system of

10mmHg in average run by heart, diaphragm/breathing, and muscle contraction, etc.

But both systems are 'mutually complimentary' only when they are with normal function; when one of two systems should lose its normal function, such mutual interdependence generates a new problem, that is, additional burdening/loading to other system. Indeed, a long term one system failure would result in a total failure of this 'inseparable' dual system altogether.

When the lymphatics themselves are damaged following initially enhanced function to compensate for the insufficient venous system, a safety valve insufficiency of lymphatic system occurs resulting lymphostasis. When the venous stasis exceeds this maximum lymphatic compensatory capacity, the insufficiency becomes 'phlebo-lymphatic' [1-4]. Therefore, such mutual interdependence between these two systems causes a new condition to affect both systems simultaneously when one of the two systems should fail to provide sufficient compensation to the other system, known as "phlebo-lymphedema" (PLE): combined condition of chronic venous insufficiency (CVI)/chronic venous hypertension and chronic lymphatic insufficiency (CLI)/chronic lymphedema.

Another words, when the CVI results in an excessive fluid load to the tissue level, giving additional load to the lymphatic system and this overloading should exceed the maximum capacity of normal lymphatic compensation, it would result in CLI disrupting check and balance function of the capillary system. When the lymphatic drainage condition is already 'compromised' by various etiologies (e.g. surgery/radiotherapy associated with cancer treatment), this CLI would become more prominent[1, 2].

Hence, the ulcer of PLE origin represents an unavoidable outcome of the joint failure of this "inseparable" venous-lymphatic circulation system, presenting as a combined condition of veno-lymphatic edema caused by CVI and CLI due to various etiopathogenesis[3, 4].

Primary PLE represents the combined condition of CVI caused mostly by marginal vein (MV)/venous malformation and CLI caused by primary lymphedema/ lymphatic malformation as the vascular malformation components of Klippel-Trenaunay syndrome. Secondary PLE is usually the outcome of deep-vein thrombosis (DVT)/postthrombotic syndrome (PTS)[5-8].

When an intravenous hypertension caused by CVI leads to an increased transcapillary filtration inside the interstitial space, the lymphatic system can compensate this fluid overload by increasing its drainage easily in its early stage. But, whenever the filtration overwhelms the lymphatic transport capacity, this combination of venous and lymphatic dysfunction would result in an interstitial fluid accumulation, thus generating the so-called PLE[9,10].

Indeed, CVI causes the greater permeability of blood capillaries to allow further extravasation of proteins to the interstitium, and the proteins now in the interstitial space with their associated oncotic pressures would lead a cascade of events of the tissue damage together with the diapedesis of red blood cells through already widened interendothelial junctions by leukocyte diapedesis[11].

Venous hypertension is not the only cause of CLI. It can be caused also by other pathologies causing peripheral oedema like congestive heart failure, nephrotic syndrome, liver cirrhosis.

So, the PLE can be further defined as the condition of 'insufficiency of the venous and lymphatic system both', in combination with possible systemic contributors, leading to accumulation of interstitial 'protein-rich' fluid in the interstitial space. A low-protein PLE is initially formed but the interstitial fluid is further comprised by a high-protein edema when the lymphatic system becomes severely deranged.

PLE is due to a combination of both dynamic insufficiency and mechanical insufficiency. But the inability of the lymphatic system to drain the fluid overload is initially a 'dynamic' insufficiency and a 'mechanical' insufficiency will soon follow/develop to initiate a vicious cycle to reduce the transport capacity to cause further damage to the lymphatic system. Systemic factors contributing to the swelling can increase the dynamic insufficiency and mechanical insufficiency can occur from trauma, surgery, radiation, damaged lymphatics from previous infections, and so forth[12-14].

Failure of appropriate lymphatic drainage would lead to an interstitial fluid hypertension which subsequently enhances the pro-inflammatory state which was already triggered by the ulcer environment. Indeed, an impairment of the lymphatic system can have a crucial influence on venous ulcer pathophysiology and consequent management[15, 16].

When the lymphatic system becomes damaged (mechanical insufficiency) or the ultrafiltrate load becomes greater than the ability of the lymphatic system to drain it (dynamic insufficiency), the lymphatic system would fail to handle the interstitial fluid load, and the proteins and macromolecules start to accumulate in the interstitium.

These proteins have their own oncotic pressures holding water molecules with them to create a swollen extremity as a 'dynamic' insufficiency since the fluid load has exceeded the lymphatic maximum transport capacity to lead to clinical development of PLE. This 'presence of proteins in the interstitial space' further induces an

inflammatory cascade to create a proinflammatory state leading to the irreversible changes seen in late stages of lymphedema[17].

Indeed, accumulation of these proteins leads to inflammatory processes to make the skin more vulnerable to the skin breaks to allow easy introduction of bacteria, which propagate quickly through the protein-rich interstitial space. These proteins may serve further as a substrate for microorganisms to facilitate extending and intensifying infections.

Increased scarring and trauma by these infections cause further damage to the vulnerable lymphatic collectors. Damage to the lymphatic system further decreases the body's ability to drain lymphedema fluid. Thus, remaining lymphatics get a stairstep type damage by repeated infections resulting in a clinically downward spiral worsening lymphedema with each additional infection[12].

Besides infection, all other identified risk factors for venous leg ulcers healing failure (e.g. interstitial fluid hypertension, metalloproteinase unbalance, and fibrosis) are also affected by an impaired lymphatic drainage[18-20].

The pathogen proliferation, enhanced in the protein-rich interstitium, is further favored by the diminished lymphatic drainage of the same bacteria and of their related by-products, as Gianesini S, et al described on the status/ role of the interstitium for the 'ulcer pathogenesis' [18]. The same infection propagation into the lymphatic system can further aggravate the lymphatic damage, so establishing a self-propagating cycle of disease progression.

Therefore, lymphatic system can be easily damaged not only by drainage overload but also by the inflammatory environment created by the fluid stasis so that this vicious circle created by the impairment of the venous and lymphatic system would cause the ulcer management more seriously complicating[21, 22].

The increase in interstitial fluid pressure can compress the capillaries even physically further to reduce nutritive tissue perfusion and also tissue hypoxia. This tissue hypoxia is further worsened by fibrin cuff formation that follows the increased inflammatory state, promoting fibrinogen leakage[18].

Degenerative phlebo-lymphatic process is therefore, mandated for early aggressive management to avoid dystrophic ulcers and skin infections, etc. PLE ulcer is therefore unavoidable 'final' outcome of 'simultaneous' failure of dual outflow system, when left alone without timely disposition. Indeed, venous ulceration is the end-stage consequence of venous hypertension, often associated with inflammation and consequent leukocyte activation and remodeling of the extracellular matrix. The same inflammatory products have a main role in deteriorating venous system function, so triggering a vicious circle of impairment[23].

Thus, as we previously advocated through JTAVR 2019;4(2):33-38 for the 'stasis ulcers' as a chronic condition of combined venous and lymphatic insufficiency: Phlebo-lymphedema (PLE)[24], we consider PLE ulcer is a payoff for such unique condition of these two interconnected venous and lymphatic systems as 'inseparable' outflow networks with mutual interdependence since their mutually complimentary function is limited only when both systems are in normal physiologic condition to provide sufficient compensation[24, 25].

Hence, a precise understanding of the nature of 'indolent' venous stasis ulcers is mandated as a combined condition of veno-lymphatic edema caused by CVI and CLI of various origins[5, 24, 25]. Indeed, clinical manifestation of the PLE is extremely variable depending upon the etiology, either primary or secondary, and the degrees/ extents of the CVI and CLI; 'Primary' PLE caused by vascular malformation component of Klippel-Trenaunay syndrome (KTS) is the combined condition of CVI by the marginal vein (MV) in its majority and CLI by primary lymphedema, while 'secondary' PLE is led by the CVI as the postthrombotic syndrome (PTS) in its majority[8, 26, 27].

Therefore, all the chronic venous stasis ulcers are mandated for simultaneous evaluation of these two closely linked conditions/systems for any one of two-system assessment to assess the CVI and CLI together. The evaluation for the venous system therefore, should be considered as warranted part of chronic lymphedema assessment[24].

Clinical Assessment

Nevertheless, this unique condition of PLE is often overlooked to result in its underdiagnosis which subsequently hinder its management including the ulcer healing process. Indeed, the failure of timely recognition of 'both' venous and lymphatic drainage system insufficiency for proper disposition would affect the ulcer pathophysiology in many negative ways: interstitial fluid hypertension, mechanical damage of the lymphatic output, enhanced inflammation with consequent fibrosis and reduced oxygenation, increased infection and exudation predisposition, as Gianesini S et al described[18].

Another words, the lymphatic system assessment also has to be included in addition to a thorough investigation of entire venous system, for example, to rule out any overlooked/neglected venous lesion to result in the indolent status especially by the 'primary/congenital' origin (e.g. marginal vein/lateral embryonic vein)[28].

Besides, the presence of a systemic cause of edema (e.g. cardiac failure, renal failure, hormonal disturbances, malignant tumors) should be addressed as a part of the evaluation of an edema of the limbs, either to exclude or confirm, to conclude the general overview of diagnosis assessment together with an iatrogenic edema related to use of Ca+ antagonists, vasodilators, anti-inflammatory drugs as a 'drug-induced edema' (e.g. sirolimus-induced edema) to conclude.

There are quite a few laboratory evaluations available now for thorough assessment of the CVI and CLI involved to the PLE as we introduced through previous publication: JTAVR 2019;4(2): 33-38 for the 'stasis ulcers' as a chronic condition of combined venous and lymphatic insufficiency: Phlebo-lymphedema (PLE)[24], so that proper selection of the tests would be able to deliver accurate appraisal of overall status of PLE and its ulcer for the management.

Indeed, as Gianesini S et al also thoroughly reviewed[18], the assessment of the extent/severity of the CVI is generally sufficient with Duplex ultrasonography (DUS) alone as the test of choice but may include additional noninvasive tests/various plethysmographies and/or ascending/descending phlebography as well when indicated. For the CLI, the radionuclide lymphoscintigraphy alone is sufficient to appraise the functional status of the lymphatic system as the test of choice to delineate excessive fluid accumulation in the tissues of the limb or affected lymphatic territories[29, 30].

However, 'primary' group of PLE as 'combined' condition of CVI and CLI caused by a group of congenital vascular malformations (CVMs) warrants additional attention on proper analysis and assessment on its various CVM components involved to Klippel-Trenaunay Syndrome (KTS)[24].

Differential diagnosis between 'primary' PLE of congenital origin and 'secondary' PLE with various backgrounds is generally sufficient with non- to less-invasive tests for the appraisal of the CVI and also CLI based on the DUS, MRI, and/or CT (e.g. MV: the major venous malformation (VM)). But direct puncture phlebography with/without ascending/descending phlebography as well would be occasionally needed as a road map for the surgical intervention on these VM components of KTS in particular[7, 31].

DUS evaluation of hemodynamic status of the MV should be done simultaneously with the deep vein system because more than one third of KTS patients with the MV have a defective deep venous system (e.g. hypoplasia of femoral vein, aplasia of iliac vein) as well. Therefore, DUS should delineate the extent and severity of the reflux and outflow resistance along the deep system and also the entire length/course of MV, located supra- and sub-fascially, to be visualized together with the perforators[31, 32].

DUS leads such basic role not only for the evaluation of the venous system but also the lymphatic systems as well. Indeed, DUS can identify the volumetric and structural changes

in the lymphatic system while determining the specific reflux pattern contributing to the lower limb edema, for example. Such simultaneous evaluation helps not to neglect a lymphatic component based on the assumption that the eventually found venous abnormality is the only cause of edema[18].

Radionuclide lymphoscintigraphy remains the gold standard for the functional assessment with a very low spatial resolution; it is able to give an accurate visualization of the lymphatic system, providing both the flow dynamics and the severity of obstruction. However, the morphological evaluation for the lymphatic system might be needed for secondary PLE to exclude neoplastic pathology at lymph node level[5, 17, 33, 34].

Therefore, the CT scan with contrast medium might be needed in addition to the DUS to visualize the edema and define the size and the depth as the morphological evaluation[35, 36].

But un general CT scan has very limited value for the assessment of the lymphedema to role in malignancy identification[5].

Magnetic resonance imaging (MRI) also can provide additional anatomical data to the lymphoscintigraphic evaluation to depict nodal architecture, lymph trunk anatomy and secondary lymphedema causes. Indeed, the visualization of interstitial protein mobilization is further possible by the application of high-tech MRI method[37]. Magnetic resonance lymphangiography is now proven to be able to assessing the anatomical and functional status of the lymphatic systems, more sensitive and accurate than lymphoscintigraphy itself[38].

Fluorescent Indocyanine green lymphography is now becoming a non-invasive alternative to traditional lymphoscintigraphy but it has a limited value only for the 'superficial' lymphatics assessment[39]. Fluorescence microlymphography can visualize lymphatic capillaries with a high sensitivity and specificity to provide an excellent base for the research on the lymphatic dysfunction involved to PLE ulcer[40].

Clinical Management

Only a correct management of PLE is an effective control of the venous insufficiency first with the reduction

in the filtration overload before simultaneous venous and lymphatic systems failure create a negative synergistic effect among venous and lymphatic insufficiency[41].

Indeed, in early stage of PLE, the interstitial fluid is initially formed as a low-protein condition but when the lymphatic system becomes deranged with further damage, it will be comprised by a high-protein edema; venous edema will become irreversible when complicated by lymphatic edema because of the fixation of water by the interstitial proteins and the hypertrophy of the tissue.

Therefore, PLE is an inevitable outcome of 'interstitial edema' as the combined form of venous and lymphatic edema when the overload on this inseparable dual outflow system overwhelms the system performance, and the 'ulcer' is mostly as 'secondary' origin to start as a venous edema to become one of the worst outcomes of mismanagement of the PLE.

Hence, when PLE is left alone with no timely disposition before it falls into the total failure of this dual outflow system, it can give a serious impact to ulcer pathophysiology as well as healing by acting on the interstitial pressure, the metabolism by-product accumulation and the predisposition to infection, as Gianesini S et al reviewed thoroughly[18].

Effective control of the venous insufficiency with a priority by proper management of the venous reflux/ obstruction is therefore, the first step for the PLE management unless the lymphatics are not affected by severe complications. Indeed, the lymphatic component of PLE can be resolved if not improved from longstanding high output overload to a low output insufficiency, once the venous hypertension has been treated effectively.

Early awareness of a potentially reduced lymphatic transport is absolutely critical in the management of these PLE patients; especially for the ulcer management, special efforts must be given for the 'earliest possible' identification of lymphatic involvement in the evaluation of the ulcer so that its management can proceed accordingly with no delay with adequately chosen treatment to venous failure/CVI to relieve the interstitial overload on the lymphatic system with priority.

Hence, decongestive lymphatic therapy (DLT) is essential for the lymphatic function restoration, as Gianesini et al emphasized[18]. Proper mobilization of the proteins out of tissue will be facilitated by Manual Lymph Drainage (MLD), which effectively disposes the proteins into the lymphatic system, where they are disposed of.

Indeed, a simple compression will only concentrate the proteins further in the interstitium by removing some of the water and the remaining proteins will hold onto water molecules. Therefore, such proper management to help the protein-rich fluid out of tissue back into remaining functional lymphatics is crucial. Indeed, the treatment of lymphedema with compression alone is not highly efficient to reduce limb volumes in a long run.

Therefore, an ideal treatment for the lymphatic component of PLE should be based on the DLT with proper combination of various types of limb compression and MLD and/or sequential intermittent pneumatic compression (SIPC) and adequate life-style in addition when indicated with other conservative therapeutic measures[4, 5, 42-45]. Indeed, SIPC is known to increase healing rates of venous ulcers compared with hosiery alone. SIPC device implied to the management of venous insufficiency has shown significant increases of venous flow among CEAP Classification 3 to 6 venous insufficiency so that the use of SIPC for the treatment of venous leg ulcers can improve the treatment when other conservative measures fail[46].

Rasmussen JC, et al also reported the outcome of the assessment on lymphatic transport in patients with CVI and venous leg ulcers following a single session of SIPC; using near-infrared fluorescence lymphatic imaging (NIRFLI) technology, they reported visible confirmation of lymphatic dysfunction at an 'early' stage in the etiology of venous ulcer formation and demonstrated lymphatic impact of SIPC with the potential therapeutic mechanism in removing excess fluid to restore fluid balance through proximal movement of lymph and interstitial fluid with the value in hastening venous ulcer healing[47].

Therefore, the compression component in various forms is the cornerstone of this DLT based treatment: bandaging, elastic stockings and intermittent pneumatic compression. Short-stretched compression bandage can maximize the muscle pump effect on the venous and lymphatic drainage in comparison to elastic ones.

However, graduated elastic stockings of the proper compression level and size remain the mainstay of phlebo-lymphedema management, significantly impacting both the outcome and its maintenance, especially after the ulcer resolution to reduce its recurrence risk[48].

Nevertheless, compression per se can remove the interstitial fluid accumulated by venous and lymphatic insufficiency only, so increasing the interstitial protein concentration. Hence, an ideal PLE management regimen requires MLD as a part of DLT to mobilize the protein-rich fluid from the tissue back into the lymphatics to help further improvement of the healing of venous leg ulcers[49].

Primary PLE

This unique 'primary' group of PLE condition presents clinically as 'combined' condition of CVI and CLI

as previously described as above, caused by a group of CVMs often represented by KTS[28, 50, 51].

Among multiple CVM components of the KTS, 'MV/ lateral embryonic vein' is the most common VM to cause CVI with venous reflux/hypertension, followed by deep vein dysplasia (e.g. iliac vein agenesis, hypoplastic femoral vein) or defective vein (e.g. web, stenosis, aneurysm, ectasia) with venous outflow obstruction/hypertension. At the same time, CLI is mostly due to 'primary lymphedema by truncular lymphatic malformation (LM) lesion (e.g. lymphatic dysplasia: aplasia, hypoplasia, or hyperplasia). But extratruncular LM (lymphangioma) also seldom involved to the CLI[6, 22, 32].

When the MV causes substantial CVI while primary lymphedema by LM causes CLI, these two combined conditions exert synergistic impacts to mutually interdependent and inseparable veno-lymphatic system to make the condition/the limb swelling worse, further to cause an 'indolent ulcer'. Therefore, MV should be treated as early as possible, preferably with surgical resection before it causes DVT with/without PE (pulmonary embolism) to resulting in CVI to become the source of PLE 'ulcer'[22, 31, 51, 52].

But it has to be carried on only when the deep venous system is normal with no evidence of defective development along iliac-femoral vein system in various defective conditions (e.g. femoral vein hypoplasia; iliac vein aplasia; intraluminal web/spur/stenosis, etc). If the removal of MV should be carried on, ignoring this 'coexisting' truncular VM lesions, a tremendous overloading to this 'defective' deep system with limited capacity to handle will encounter potential risk of 'venous gangrene'.

Besides, MV often runs along the lateral aspect of the leg, usually very superficially beneath the skin with a minimum soft tissue coverage mimicking the ordinary varicose veins. But the MV is NOT a varicose vein but an embryonic vein remnant which failed to involute to remain as a birth defect following the developmental arrest during the vein trunk formation period in the 'later stage' of the embryonic development.

Hence, MV accompanies a unique condition of congenital absence/lack of venous valves as well, known as the avavulosis/avalvulia, allowing a severe reflux resulting in chronic venous hypertension/stasis with subsequent CVI and postthrombotic syndrome (PTS). And also, abnormal vessel wall structure with defective/deficient media of the vein wall with lack of smooth muscle layers (cf. varicose vein) carries a high risk of the intravascular thrombosis resulting in VTE (venous thrombo-embolism) in addition to severe CVI and PTS through the rest of life[7, 8, 31].

Besides, there are another VM lesion can coexist as one of VM components of KTS, termed as 'extratruncular' type as the outcome of defective development along the 'earlier' stage of embryogenesis, since MV is also another type of VM as 'truncular' lesion with direct involvement to the venous vessel trunk itself as the outcome of defective development along the 'later' stage of embryogenesis[8, 53, 54].

The cause of lymphatic dysfunction will also have to be assessed thoroughly for this primary PLE group, for two different types of lymphatic malformation (LM), that is, lymphangioma/ extratruncular type and primary lymphedema/truncular type, which might exist together as the vascular malformation component of KTS together with the VM[5, 55].

Often, many considers primary lymphedema as one and only LM lesions involved to KTS but infrequently 'lymphangioma' lesions also get involved and overlooked to become the source of the infection/sepsis while dealing the PLE ulcer or MV. Hence, a thorough search for these two different types of the LM lesions should be carried on simultaneously together with the VM evaluation[5, 6].

Hence, proper identification of each CVM component involved to the CVI as well as CLI is essential for all the primary PLE investigation with/without the ulcer.

Secondary PLE

Secondary PLE develops, as explained previously, mostly as the sequalae of PTS following the DVT along the end stage of CVI, and its CLI is generally secondary regional/local lymphedema following steady progress of the local tissue damage (e.g. ulcer) by the CVI/PTS.

Therefore, the secondary PLE becomes relatively complicated condition to manage newly added condition of local/regional lymphedema to cause CLI, although the management of its CVI is less complicated in comparison to primary PLE in terms of etio-pathophysiology point of view. CVI by the PTS can be further improved with correction of the venous outflow obstruction with angioplasty & stent, for example.

However, this new lymphatic dysfunction with visibly strained lymphatic system, as a victim of abnormal venous condition, becomes a major burdening to its management as a whole due to the complexity of local circulation. Hence, proper assessment of the lymphatic system is also warranted for the clinical management of this group of secondary PLE ulcer.

Nevertheless, occasionally, clinical/subclinical condition of primary lymphedema is also involved as the cause of CLI to accelerate the deterioration of the underlying benign primary venous disorder (e.g. reflux) to result in CVI when overlooked[26, 27, 36].

Summary

Whenever the filtration overwhelms the lymphatic transport capacity for mutual potential compensation, an interstitial fluid accumulation occurs as the consequence of close interconnection among venous and lymphatic systems thus generating the so-called phlebolymphedema: a combination of venous and lymphatic dysfunction[10, 56].

Whenever the filtration overwhelms the lymphatic transport capacity to result in fluid accumulation, the failure of appropriate lymphatic drainage would follow and an interstitial fluid hypertension would develop and enhance the pro-inflammatory state that was already triggered by the ulcer environment.

Because of the inability of the lymphatic system to drain the fluid overload, a dynamic insufficiency occurs initially but a mechanical insufficiency would soon follow when the lymphatics are further damaged by various physical as well as biochemical factors: inflammation, surgery, radiotherapy, trauma, infections[17, 36].

Toxic by-products of cellular metabolism will be therefore accumulated and consequently fibrosis is promoted to make oxygen and other nutrient diffusion further impeded. This tissue hypoxia is further aggravated by fibrin cuff formation that follows the increased inflammatory state, promoting fibrinogen leakage. The lack of absorption of metabolic by-products creates a further aggravation in the pathological process[57-59].

Hence, interstitial fluid hypertension, metalloproteinase unbalance, fibrosis and infections are all affected by an impaired lymphatic drainage to become risk factors for venous leg ulcers healing failure. Therefore, the lymphatic system can be easily damaged both by drainage overload and by the inflammatory environment created by the fluid stasis. Such impairment of the venous and lymphatic system would create a vicious circle to cause the ulcer management seriously complicating[1, 20].

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