

## Inflammation and compression: the state of art

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Chronic venous leg ulcer affects around 1-2% of the adult population in the western world,<sup>1</sup> with significant expenditures and high social and economic impact. The leading hemodynamic cause is represented by venous hypertension, affecting the venous macro- and micro-circulation, which is able to induce morphologic, functional and biochemical alterations in postcapillary venules and in the surrounding tissue microenvironment.<sup>2</sup>

In this regard, inflammatory processes by leukocytes and macrophages affect the venous endothelium, promoting a complex succession of events involving the activation of adhesion molecules, chemokines, cytokines, growth factors, and proteases which cause endothelial dysfunction and dysregulation, compromising tissue integrity and finally lead to dermal damage and ulcer development.<sup>3</sup>

A critical aspect for treating venous leg ulcer is correcting the abnormal venous hemodynamics by compression therapy. In fact, compression therapy has been widely recognized as the cornerstone in the management of chronic venous insufficiency (CVI), clinical condition resulting from venous hypertension secondary to superficial or deep venous valvular reflux and/or obstruction.<sup>4</sup> Compression can be achieved using compression bandaging, compression pumps, or graduated compression stockings, which, by decreasing ambulatory venous hypertension in the area, counteract the chronic inflammation in the tissues and finally aide healing processes.<sup>5</sup>

It has been shown that ulcer dressings create and maintain a moist environment on the ulcer surface, promoting autolytic debridement, angiogenesis and a more rapid formation of granulation tissue, favoring keratinocytes migration and finally accelerating healing of wounds, even if different wound dressings must be used according to the ulcer stages.<sup>6</sup>

In the recent revision of the Society for Vascular Surgery and American Venous Forum guidelines on management of venous leg ulcers performed by the International Union of Phlebology, it has been highlighted that ... *in a patient with a venous leg ulcer without arterial involvement or peripheral neuropathy, it is recommend strong compression pressure (>40 mmHg resting pressure at the ankle) over low compression pressure to increase venous leg ulcer healing rate...* suggesting Grade 1 and

Level of Evidence B.<sup>7</sup> Moreover, it has been provided evidence that strong (>40 mmHg) compression is more effective than low (<20 mmHg) compression in promoting ulcer healing, including also that ... *in a patient with a healed venous leg ulcer, the compression therapy decreases the risk of ulcer recurrence...* (Grade 2 and Level of Evidence B).<sup>7</sup>

Unfortunately, venous leg ulcer recurrence ranges between 30-70%, and other modalities in therapy along with the compression therapy are required. The goal for adjuvant products is to promote the shift from an inflammatory chronic wound to a reparative wound that will promote provisional extracellular matrix deposition and re-epithelialization.

There are many products on the market that can be used as adjuvants to compression therapy; in this respect, it has been highlighted that ... *for long-standing or large venous leg ulcer, we recommend treatment with either pentoxifylline, micronized purified flavonoid fraction or sulodexide, all used in combination with compression therapy* (Grade 1; Level of Evidence B);<sup>7</sup> however, it must be recognized that there is a paucity of clinical trials that have evaluated the clinical effectiveness of specific products with clearly defined end points, and most importantly a healed venous leg ulcer with a low recurrence rate. Despite the treatment modalities are aimed at reducing venous hypertension, some therapies, although widely used, only provide short-term improvement of the edema but do not provide long-term benefits.<sup>8</sup>

Chronic venous disease and CVI are characterized by an increase in ambulatory venous pressure but the different symptoms and signs clearly show that there is an inflammatory state secondary to venous hypertension, which leads to venous wall and valves injury.<sup>1</sup>

Several studies were performed to assess and demonstrate the efficacy of compression treatment in the management of chronic venous leg ulceration. An interesting randomized controlled trial published in 2004, comparing compression treatment alone or in combination with superficial venous surgery, demonstrated that 24-week healing rates were similar in the compression-surgery *vs.* compression alone groups, but 12-months ulcer recurrence rates were significantly reduced in the compression-surgery patients, suggesting, from a clinical point of view, that most patients with chronic venous ulceration will benefit from the combination of therapies added to simple surgery.<sup>9</sup> It has also been demonstrated that significantly less legs in the compression-surgery treated patients developed perforator incompetence in comparison to the group treated with compression alone, offering more protection against developing new perforator incompetence.<sup>10</sup>

Although a plethora of studies have identi-

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Veins and Lymphatics 2016; 5:5980  
doi:10.4081/vl.2016.5980

fied up-regulation of various pro-inflammatory cytokines in fluid collected from venous leg ulcers,<sup>11</sup> and even if the compression therapy results in healing of most venous leg ulcers, the biomolecular mechanism(s) responsible for this effect is not well understood.

In this respect, an interesting study performed on biopsies from ulcerated tissue from non-healing chronic venous insufficiency affected patients treated with high-compression therapy revealed that compression therapy (with 3-layer or 4-layer compression bandage system for 4 weeks) resulted in healing coupled with reduced pro-inflammatory cytokines [*e.g.*, interleukin (IL)-1, interferon- $\gamma$ , granulocyte-macrophage colony-stimulating factor] and higher levels of the anti-inflammatory cytokine IL-1RA.<sup>12</sup> Similarly, it has been previously reported that wound healing of venous ulcers treated with compression therapy correlated with decreasing serum levels of tumor necrosis factor- $\alpha$  and vascular endothelial growth factor<sup>13</sup> and increasing exudate levels of transforming growth factor- $\beta$  1.<sup>14</sup>

Moreover, it is well known that an alteration of the proteolytic and anti-proteolytic balance is significantly implicated in chronic wound initiation and progression. In this regard, it has been investigated in venous leg ulcer tissues the effect of sustained limb compression of 30 mmHg (or greater) for 4 weeks on ulcer healing rates, demonstrating that stromelysin matrix metalloproteinase (MMP)-3, collagenase MMP-8 and gelatinase MMP-9 were significantly reduced after the compression treatment, and suggesting that a down-regulation of proteinases in ulcer tissue microenvironment by compression may represent a possible mechanism (in conjunction to the decrease of inflammation) to counteract the progression of CVI and improve venous ulcer healing.<sup>15</sup> More recently, it has been reported that venous ulcers treated with a multi-layer bandaging system showed decreased plasma levels of MMP-9, TIMP-1, and MMP-2/TIMP-2 ratio in healed wounds.<sup>16</sup>

Finally, a recent randomized placebo-controlled trial assessed the efficacy of elastic compression stocking to prevent post-throm-

botic syndrome; although the study showed several bias weakening the entire protocol, their results suggested that elastic compression did not prevent post-thrombotic syndrome, not supporting routine wearing of elastic compression stocking after deep vein thrombosis.<sup>17</sup> Noteworthy is the scarce presence of biomolecular evidence of elastic compression efficacy on swelling and inflammation, suggesting that further studies are needed to clarify the mechanisms of stocking efficacy in down-regulation of hemodynamic and inflammatory processes implicated in CVI and deep venous thrombosis.

For what concerns the future perspectives, on the basis of previous studies performed in animal models<sup>18</sup> and human cell lines,<sup>19,20</sup> it is noteworthy that glycosaminoglycans in conjunction to compression therapy may improve ulcer healing,<sup>21</sup> due to their effectiveness in down-regulating the release of cytokines, chemokines and leukocyte colony stimulating factors from human macrophages and in modulating the inflammatory pathways. The effects of glycosaminoglycans could actually enhance the effects of compression therapy on inflammation mediators.

## References

- Raffetto JD, Mannello F. Patho-physiology of chronic venous disease. *Int Angiol* 2014;33:212-21.
- Raffetto JD. Which dressings reduce inflammation and improve venous leg ulcer healing. *Phlebology* 2014;29:157-64.
- Mannello F, Raffetto JD. Matrix metalloproteinase activity and glycosaminoglycans in chronic venous disease: the linkage among cell biology, pathology, and translational research. *Am J Transl Res* 2011;3:149-58.
- Kolluri R. Management of venous ulcers. *Tech Vasc Interv Radiol* 2014;17:132-8.
- Carr SC. Diagnosis and management of venous ulcers. *Perspect Vasc Surg Endovasc Ther* 2008;20:82-5.
- Mosti G. Wound care in venous ulcers. *Phlebology* 2013;28:79-85.
- Mosti G, De Maeseneer M, Cavezzi A, et al. Society for Vascular Surgery and American Venous Forum Guidelines on the management of venous leg ulcers: the point of view of the International Union of Phlebology. *Int Angiol* 2015;34:202-18.
- Raffetto JD, Eberhardt RT, Dean SM, et al. Pharmacologic treatment to improve venous leg ulcers healing. *J Vasc Surg Venous Lymphatic Disorder* 2015 [Epub ahead of print].
- Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomized controlled trial. *Lancet* 2004;363:1854-9.
- Gohel MS, Barwell JR, Wakely C, et al. The influence of superficial venous surgery and compression on incompetent perforators in chronic venous leg ulceration. *Eur J Vasc Endovasc Surg* 2005;29:78-82.
- Mannello F, Ligi D, Canale M, Raffetto JD. Omics profiles in chronic venous ulcer wound fluid: innovative applications for translational medicine. *Exp Rev Mol Diagn* 2014;14:737-62.
- Beidler SK, Douillet CD, Berndt DF, et al. Inflammatory cytokine levels in chronic venous insufficiency ulcer tissue before and after compression therapy. *J Vasc Surg* 2009;49:1013-20.
- Murphy MA, Joyce WP, Condron C, Bouchier-Hayes D. A reduction in serum cytokine levels parallels healing of venous ulcers in patients undergoing compression therapy. *Eur J Vasc Endovasc Surg* 2002;23:349-52.
- Gohel MS, Windhaber RA, Tarlton JF, et al. The relationship between cytokine concentrations and wound healing in chronic venous ulceration. *J Vasc Surg* 2008;48:1272-7.
- Beidler SK, Douillet CD, Berndt DF, et al. Multiplexed analyses of matrix metalloproteinases in leg ulcer tissue of patients with chronic venous insufficiency before and after compression therapy. *Wound Repair Regen* 2008;16:642-8.
- Caimi G, Ferrara F, Montana M, et al. Behaviour of the plasma concentration of gelatinases and their tissue inhibitors in subjects with venous leg ulcers. *Clin Hemorheol Microcirc*. 2015;60:309-16.
- Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomized placebo-controlled trial. *Lancet* 2014;383:880-8.
- Tong M, Tuk B, Hekking IM, et al. Heparan sulphate glycosaminoglycan mimetic improves pressure ulcer healing in a rat model of cutaneous ischemia-reperfusion injury. *Wound Repair Regen* 2011;19:505-14.
- Mannello F, Medda V, Ligi D, Raffetto JD. Glycosaminoglycan sulodexide inhibition of MMP-9 gelatinase secretion and activity: possible pharmacological role against collagen degradation in vascular chronic diseases. *Curr Vasc Pharmacol* 2013;11:354-65.
- Mannello F, Ligi D, Canale M, Raffetto JD. Sulodexide down-regulates the release of cytokines, chemokines and leukocyte colony stimulating factors from human macrophages: role of glycosaminoglycans in inflammatory pathways of chronic venous disease. *Curr Vasc Pharmacol* 2014;12:173-85.
- Mannello F, Ligi D, Raffetto JD. Glycosaminoglycan sulodexide modulates inflammatory pathways in chronic venous disease. *Int Angiol* 2015;33:236-42.