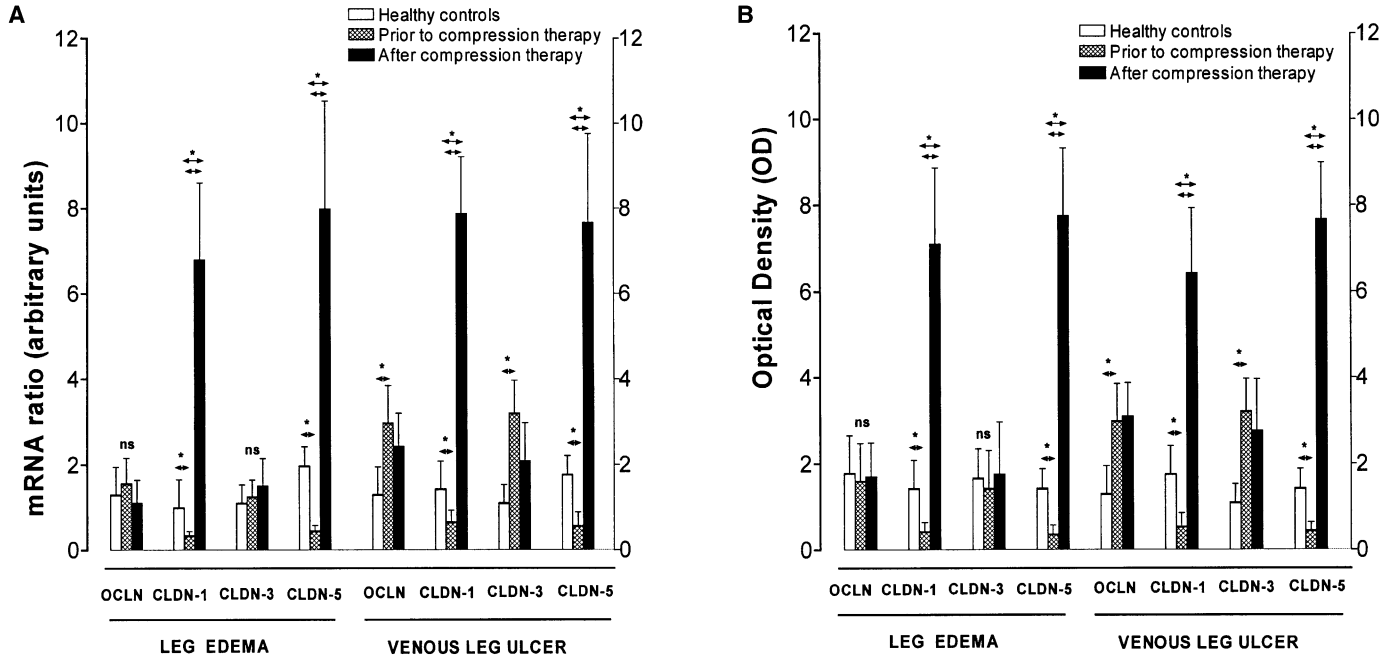

Figure 1. Elevated expression for CLDN-1 and CLDN-5 on mRNA- (A) and protein level (B) after compression therapy in patients with chronic venous insufficiency (A) Densitometric evaluation of generated mRNA-products of OCLN, CLDN-1, CLDN-3 and CLDN-5 in healthy controls (white bars), edema patients prior to treatment (crossed bar) and after treatment (black bars). (B) Densitometirc evaluation of immunoblots of OCLN, CLDN-1, CLDN-3 and CLDN-5 in healthy controls (white bars), venous leg ulcer patients prior to treatment (crossed bar) and after treatment (black bars). Data are means ± SEM (n = 8 for healthy skin; n = 8 for edema group; n = 8 for leg ulcer group). The significance of difference was determined by an unpaired student's t test. Differences were considered significant at $^{*}p < 0.01$.

from the expression of healthy controls as well as patients prior to treatment. Whether up-regulation of tight junction molecules can be directly associated with the mode of treatment requires further investigations. Compression therapy may tighten the paracellular barrier via elevated expression of specific tight junctions and may prevent the progression of chronic venous insufficiency due to inhibited permeability of fluid into the perivascular tissue.

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REFERENCES

Fletcher A, Cullum N, Sheldon TA: A systematic review of compression treatment for venous leg ulcers. *BMJ* 315:576–580, 1997

Herouy Y, May AE, Pornschlegel G, *et al*: Lipodermatosclerosis is characterized by elevated expression and activation of matrix metalloproteinases: Implications for venous ulcer formation. *J Invest Dermatol* 111:822–827, 1998

Pierson S, Pierson D, Swallow R, Johnson G Jr: Efficacy of graded elastic compression in the lower leg. *JAMA* 249:242–243, 1983

Tsukita S, Furuse M: Pores in the wall: claudins constitute tight junction strands containing aqueous pores. *J Cell Biol* 149:13–16, 2000

Tsukita S, Furuse M, Itoh M: Multifunctional strands in tight junctions. *Nat Rev Mol Cell Biol* 2:285–293, 2001

Tsukita S, Furuse M, Itoh M: Structural and signalling molecules come together at tight junctions. *Curr Opin Cell Biol* 11:628–633, 1999

Valencia IC, Falabella A, Kirsner RS, Eaglstein WH: Chronic venous insufficiency and venous leg ulceration. *J Am Acad Dermatol* 44:401–421, 2001

Inhibition of Vascular Cell Adhesion Molecule-1 Expression in Human Dermal Microvascular Endothelial Cells by Iron Chelators

To the Editor:

Koo *et al* (2003) recently reported that iron chelators inhibit tumor necrosis factor-α-mediated vascular cell adhesion molecule-1 expression in human dermal microvascular endothelial cells, suggesting that iron plays a critical role in tumor necrosis factor-α-mediated vascular cell adhesion molecule-1 induction in these cells. As outlined by the authors, these findings may provide new insights into the role of iron in the pathogenesis of cutaneous inflammatory disorders, such as psoriasis, contact dermatitis, and ultraviolet-induced skin changes. They also support previous studies demonstrating that topically applied iron chelators provide a high level of photoprotection in both animal and human testing (Bissett *et al*, 1994).

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Nevertheless, it may be regrettable to restrict the implication of these important results to inflammatory disorders. The adhesive function of vascular cell adhesion molecule-1 not only facilitates the binding of leukocytes to activated endothelial cells but is also used by cancer cells to enhance metastatic implantation and spread (Rice and Bevilacqua, 1989; Vidal-Vanaclocha *et al*, 2000). Moreover, vascular cell adhesion molecule-1 is closely associated with angiogenesis (Nakao *et al*, 2003). Iron has also been implicated in the pathogenesis, of cancers and several clinical observations have been made linking cellular iron content to the development of cancers in humans (Weinberg, 1996). The metal is carcinogenic owing to its catalytic effect on the formation of hydroxyl radicals, suppression of the activity of host defense cells, and promotion of cancer cell multiplication (Weinberg, 1996). Based on this possible role of iron in tumor development, several studies have suggested a potential antitumor activity of iron chelation and have shown that iron deprivation induces apoptosis of various proliferating cell types (Richardson, 2002; Simonart *et al*, 2002). We previously showed that exposure of human dermal microvascular endothelial cells to the iron chelator 10 to 100 μM desferrioxamine for less than 24 h did not significantly reduce the number of cells excluding Trypan blue dye (Simonart *et al*, 2000), which is in line with the results reported by Koo *et al* (2003). Nevertheless, this significantly affected the clonogenic survival of human dermal microvascular endothelial cells (Simonart *et al*, 2000), indicating a possible latent toxicity of the drug, which was evidenced by massive apoptosis of the cells after 72 h of exposure to desferrioxamine at concentrations 10 times lower than those used by Koo and colleagues. Because inflammatory endothelial responses may be inhibited during apoptotic stimuli (Neuzil *et al*, 2001), it remains to be determined whether distinct mechanisms are responsible for the anti-inflammatory and pro-apoptotic effects of iron chelators in endothelial cells. Nevertheless, the results reported by Koo *et al* may further suggest that the investigation and development of iron chelators as anticancer agents is warranted.

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REFERENCES

Bissett DL, Oelrich DM, Hannon DP: Evaluation of a topical iron chelator in animals and in human beings: Short-term photoprotection by 2-furildioxime. *J Am Acad Dermatol* 31:572–578, 1994

Koo SW, Casper KA, Otto KB, Gira AK, Swerlick RA: Iron chelators inhibit VCAM-1 expression in human dermal microvascular endothelial cells. 120:871–879, 2003

Nakao S, Kuwano T, Ishibashi T, Kuwano M, Ono M: Synergistic effect of TNF-alpha in soluble VCAM-1-induced angiogenesis through alpha (4) integrins. *J Immunol* 170:5704–5711, 2003

Neuzil J, Schroder A, von Hundelshausen P, Zernecke A, Weber T, Gellert N, Weber C: Inhibition of inflammatory endothelial responses by a pathway involving caspase activation and p65 cleavage. *Biochemistry* 40:4686–4692, 2001

Rice GE, Bevilacqua MP: An inducible endothelial cell surface glycoprotein mediates melanoma adhesion. *Science* 246:1303–1306, 1989

Richardson DR: Therapeutic potential of iron chelators in cancer therapy. *Adv Exp Med Biol* 509:231–249, 2002

Simonart T, Boelaert JR, Mosselmans R, Andrei G, Noel JC, De Clercq E, Snoeck R: Antiproliferative and apoptotic effects of iron chelators on human cervical carcinoma cells. *Gynecol Oncol* 85:95–102, 2002

Simonart T, Degraef C, Andrei G, *et al*: Iron chelators inhibit the growth and induce the apoptosis of Kaposi's sarcoma cells and of their putative endothelial precursors. *J Invest Dermatol* 115:893–900, 2000

Vidal-Vanaclocha F, Fantuzzi G, Mendoza L, *et al*: IL-18 regulates IL-1beta-dependent hepatic melanoma metastasis via vascular cell adhesion molecule-1. *Proc Natl Acad Sci USA* 97:734–739, 2000

Weinberg ED: The role of iron in cancer. *Eur J Cancer Prev* 5:19–36, 1996