

Beethoven Saal

16.00–17.30

# V 16

## Compression Therapy in Wound Care

### Kompressionstherapie in der Wundversorgung

V 16-2

#### Results of randomized and controlled studies on compression therapy

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**Background:** Among the numerous indications for medical compression therapy venous ulceration is the field where the highest number of randomized controlled trials (RCT's) is available proving its clinical efficiency.

**Aim:** To give an overview on the existing RCT's on leg ulcer healing and to discuss some deficiencies and questions, which should be considered in future trials. **Methods** The collection of RCT's and systematic reviews is mainly based on the last Cochrane review<sup>1</sup> and on the report of an International Consensus Meeting on "evidence based compression therapy"<sup>2</sup>. Additionally new trials from the last two years are also taken into consideration.

**Results:** Compression is beneficial in ulcer healing compared to no compression. Multi-layer bandages exerting a higher interface pressure aid healing better than single layer. Conflicting results have been reported concerning different compression materials (elastic, long stretch versus non-elastic, short stretch material, compression stockings). Some of the controversies can be explained by different compression techniques, different skill and various training-levels of the bandagers.

**Conclusions:** The hemodynamic efficacy of compression therapy in patients with venous ulcers is associated with the healing rate and depends largely upon the amount of compression during rest and while walking. In order to obtain a fair comparison between different compression materials, future RCT's should consider compression pressure and stiffness of the final bandage on the individual leg, which can be measured by relative simple methods.

#### References

1. **Cullum N, Nelson EA, Fletcher AW, Sheldon TA.** Compression for venous leg ulcers. The Cochrane Database of Systematic Reviews 2001, Issue 2.
2. **Partsch H.** Evidence based compression. VASA 2003;32: Suppl. 63.

V 16-3

#### Conclusions from the Bonn vein essay for the medicine

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Chronic venous disorders are among the most common diseases in Germany. In the Tübingen Study, conducted in 1979, every eighth adult suffered from severe chronic venous disease. Reliable data on the current situation in Germany was not available. Therefore, the German Society of Phlebology initiated an epidemiologic study to evaluate the prevalence and risk factors of chronic venous diseases in the general population. The study was supported by the Ministry of Health. From October 2000 to March 2002, 3072 members of the general population of the city of Bonn and two rural townships, aged 18–79 years were taken part in this study (1350 men, 1722 women). Participants were selected via simple random sampling from the registries of residents. The participants answered a standardized questionnaire and were examined by clinical means and by duplex ultrasound. Results show a distribution in the CEAP classification with C0: 9.6 %, C1: 59.0 %, C2: 14.3 %, C3: 13.4 %, C4: 2.9 %, C5: 0.6 % and C6: 0.1 %, when considering the highest class of each individual. Reflux in the superficial or deep venous system was discovered by duplex scan in 28 % of the population. A venous operation had previously been performed on 6.9 % of participants and sclerotherapy had previously been performed on 5.5 %. 14.6 % had worn compression stockings in the past. The percentage of skin-changes due to chronic venous disorder was significantly lower than in the Tübingen-Study. Main risk factors for Varicose veins are: genetic predisposition, pregnancies, obesity, female gender and age. In CVI obesity is a higher risk factor and arterial hypertonus, lower social class and living in the city are additional risks. The results of this study indicate a high prevalence of chronic venous diseases in Germany. Risk factors for chronic venous diseases are different in varicose veins and in chronic venous insufficiency.

Schiller Saal

16.00–17.30

## V 17

### *Adhesion Molecules, Chemokines and Proinflammatory Cytokines, Shaping, Blistering and Wound Healing I*

### **Adhäsionsmoleküle, Chemokine und proinflammatorische Cytokine, ? und Wundheilung I**

#### V 17-2

#### *Chemokines – mediators in cutaneous wound healing*

*B. Homey, E. Bünemann*

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Wound healing represents a dynamic process involving directional migration of leukocytes and structural cells. Chemokines control migratory processes and their critical role in leukocyte trafficking has recently been identified. So far, very little is known about their function in tissue repair. In the present study, we comprehensively analyzed the role of chemokines and their receptor in the dynamic process of cutaneous wound healing. Our results demonstrated that a subset of chemokines is among the most highly regulated genes. Structural cells of the skin expressed a distinct and functionally active receptor repertoire on their cell surface. Furthermore, corresponding chemokines markedly enhanced wound repair in vitro. Taken together, these findings provide insights into the chemokine networks during cutaneous wound healing and suggest novel strategies for the treatment of wound healing disorders.

Hegel Saal

16.00–17.30

# V 18

## *Bridging the Gap: Patient Outcomes*

## Brücken bauen: Klinische Prognose

### V 18-3

#### *Self-care by patients*

*E. A. Nelson*

**E. A. Nelson, PhD RN, Reader, School of Healthcare, Baines Wing, University of Leeds, P.O. Box 214, Leeds LS2 9UT.**

This presentation will describe the approaches to supporting self-care for people with chronic health problems and how these may lead to innovations in care for people with chronic wounds.

A number of studies have sought to describe the impact of leg ulcers on quality of life.[1-4] The findings from qualitative studies have a number of common themes: pain, managing symptoms, restrictions to activities, psychological effects, restrictions on footwear and clothing, powerlessness, contribution to care, psychological aspects, issues around the way in which ulcer care is delivered, understanding of ulceration, and uncertainty about healing, illustrating unmet needs of patients receiving nursing care.

Self-care has been defined as the activities associated with health promotion and restoring health. According to Orem's theory, self-care is characterised by conscious actions taken to regulate functioning and development for health and well-being (including managing illness or disease).[5] A number of people with chronic wounds may be able to contribute to self-care, and there is increasing evidence from trials evaluating a Chronic Disease

Self-Management Programme approach to self-care in people with asthma, arthritis, diabetes, and heart failure, for example, that they lead to improvements in patient outcomes (e.g. higher quality of life and fewer relapses) and potentially lower use of healthcare services (e.g. fewer admissions). To date, however, no studies have reported outcomes for people with chronic wounds, and the impact of such approaches in these populations is therefore not known. In considering the utility of these approaches for people with chronic wounds, it may be useful to determine what self-care is performed already, what increased self-care would consist of in a range of chronic wound populations, how clinician behaviour and service delivery impacts on self-care behaviour, if courses to support self-care are effective and if so, whether generic or condition specific courses are appropriate.

#### References

1. **Ebbeskog B, Ekman SL.** Elderly persons' experiences of living with venous leg ulcer: living in a dialectal relationship between freedom and imprisonment. *Scand J Caring Sci* 2001;15[3]: 235-43.
2. **Hyde C, Ward B, Horsfall J, Winder G.** Older women's experience of living with chronic leg ulceration. *Int J Nurs Pract* 1999;5[4]: 189-98.
3. **Rich A, McLachlan L.** How living with a leg ulcer affects people's daily life: a nurse-led study. *Journal of Wound Care* 2003;12: 51-4.
4. **Walshe C.** Living with a venous leg ulcer: a descriptive study of patients' experiences. *J Adv Nurs* 1995; 22: 1092-1100.
5. **Orem DE** (1985) *Nursing: Concepts of Practice*. Third edition. New York NY, McGraw-Hill.

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16.00–17.30

## V 43

### Young Investigator Award

## Preis der Nachwuchswissenschaftler

V 43-1

### *Design of a novel proteolysis resistant VEGF variant*

### Design einer neuen proteolyseresistenten VEGF Mutante

*D. Roth<sup>1</sup>, G. Lauer<sup>1</sup>, M. Paulsson<sup>2</sup>,  
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Vascular endothelial growth factor (VEGF) is a potent angiogenic mediator in tissue repair. Recently we demonstrated that in non-healing human wounds a plasmin-catalyzed cleavage significantly reduces the bioactivity of the VEGF-A isoform VEGF165, suggesting that VEGF165 degradation and inactivation contribute to an impaired healing response. Plasmin digestion results in loss of the carboxyl-terminal heparin-binding domain. To investigate the biological relevance of the protease sensitivity of VEGF165 during cutaneous repair, we assessed the activity of a VEGF165 mutant resistant to plasmin proteolysis (VEGF165-MutPro111) in a genetic mouse model of impaired wound healing (db/db mouse). In this mouse model the stability of the mutant VEGF165 was substantially increased in wound tissue lysates in comparison to VEGF165 wild type thus indicating a prolonged activity of the plasmin resistant VEGF165 mutant. The db/db delayed healing phenotype could be reversed by topical application of VEGF165-MutPro111 and most interestingly the resistance of VEGF165 to plasmin cleavage resulted in the increased stability of vascular structures during the late phase of healing due to delayed and reduced endothelial cell apoptosis. Our data provide the first indication that plasmin-catalyzed cleavage modulates VEGF165 mediated angiogenesis in vivo. Our experiments propose that the ability to stabilize the heparin-binding capability of VEGF165-A may help to preserve the biological function of VEGF165 under conditions in which proteases are highly active such as wound repair and inflammation.

Der vaskuläre Endothelzellfaktor (VEGF) stellt ein Schlüssel-molekül in der Regulation der Wundangiogenese dar. Wir konnten zeigen, dass VEGF165, eine Splicevariante von VEGF-A, im Milieu der chronisch nichtheilenden Wunde proteolytisch degradiert wird. Im Gegensatz dazu war VEGF165 Protein im Wundmilieu der heilenden Wunde stabil. Proteaseinhibitoranalysen und Proteinsequenzierung der VEGF165 Spaltprodukte zeigten, dass Serinproteasen, insbesondere Plasmin, an der Spaltung von VEGF im chronischen Wundmilieu beteiligt sind. Die Plasmin katalysierte Proteolyse von VEGF165 führt zu einem Verlust der Heparinbindungsdomäne und zu einer signifikanten Einbuße der biologischen Aktivität. Diese Untersuchungen veranlassten uns zur Generierung einer plasminresistenten VEGF Mutante (VEGF165-MutPro111), die sich durch eine erhöhte Stabilität im chronischen Wundmilieu humaner nichtheilender Wunden auszeichnet. Um die Bedeutung der VEGF165 Plasminsensitivität während der Wundheilung in vivo zu untersuchen, haben wir die Stabilität und Aktivität der plasminresistenten VEGF Mutante in einem genetischen Mausmodell mit verzögerter Wundheilung (db/db) untersucht. Es konnte gezeigt werden, dass die topische Applikation von VEGF165-MutPro111 die gestörten Wundheilung im db/db Modell signifikant beschleunigt. In db/db Wundlysaten war die Stabilität der VEGF Mutante gegenüber der Stabilität von VEGF165 Wildtypprotein (VEGF165-Wt) signifikant erhöht. Interessanterweise führte die Plasminresistenz zu einer erhöhten Aktivität von VEGF165 im Wundmilieu, die sich in einer verminderten Apoptoserate endothelialer Zellen im kapillarreichen Wundgewebe zeigte. Der antiapoptotische Effekt von VEGF165-MutPro111 erklärt die erhöhte Stabilität kapillärer Strukturen, die sich charakteristischerweise im Gewebe VEGF165-MutPro111, aber nicht VEGF165-Wt behandelter Wunden, zeigte. Unsere Untersuchungen zeigen erstmalig, dass in vivo die Plasmin vermittelte Spaltung von VEGF165 die Angiogenese reguliert. Unsere Untersuchungen weisen darauf hin, dass die Aktivität von VEGF165 durch eine Stabilisierung der Heparinbindungsdomäne, insbesondere in einem proteasereichen Milieu wie der chronischen Wunde, möglicherweise aber auch in anderen Entzündungsprozessen, reguliert werden kann.

## V 43-2

***Role of Shc family signaling protein in mesenchymal stem cells******K. Akino<sup>1</sup>, T. Imaizumi<sup>2</sup>, N. Mori<sup>1</sup>, A. Hirano<sup>2</sup>, S. Akita<sup>2</sup>***<sup>1</sup>Nagasaki University, Department of Developmental and Reconstructive Medicine, Nagasaki, Japan,<sup>2</sup>Nagasaki University, Department of Plastic Surgery, Nagasaki, Japan

Mesenchymal stem cells are implicated in the neurological disorders and neuronal differentiation. The neurological imbalance and abnormality may lead to impaired wound healing such as paraplegic and diabetic diseases. Mesenchymal stem cell grafting in the cutaneous wounds successfully improves the rate of the healing, however, the further mechanisms are unknown. Shc is one of intracellular signaling proteins related to various cell functions. Detail analysis of Shc in mesenchymal stem cells may implicate in neuronal and cutaneous regeneration. Shc recognizes the phosphorylation of various growth factor receptors and the activated signals are transported to Ras-ERK or JNK via Grb2-SOS. Therefore, Shc is the cytosolic protein involves in cell proliferation, cell differentiation, and induction of apoptosis. Among Shc family, ShcC/Neuronal Shc (N-Shc) is one of the homologues of Shc proteins and demonstrated the neuron-specific actions. Human mesenchymal stem cells (hMSCs), which is distinctively sorted by cell surface antigens and the cell properties and bone marrow stromal cell derived from ShcC deleted mice are further analyzed in vitro and in vivo. Various neuronal markers such as Shc family and stathmin-related proteins are investigated. The hMSCs demonstrated immunoreactivities in SCG10 and OP-18(stathmin) in cytoplasm, whereas there were only Shc and ShcC cytoplasmic immunoreactivities but not in Sck, which is specific to membrane depolarization. The immunoreactively positive cells were all blackout in the nuclei, in which DAPI immunoreactivities were also observed. The RT-PCR transcript levels normalized by the internal G3PDH control demonstrated the SCG10 SCLIP transcripts in hMSCs. Since the stathmin (OP-18) antibody used for immunocytochemistry was not able to distinguish stathmin antigen from related antigens such as SCLIP and Rb3, the detail profile of the gene products first elucidated by RT-PCR. SCG10, SCLIP and stathmin were detectable but not RB3. The expression levels of SCG10 and SCLIP in hMSCs were cell-cycle dependent ( $p < 0.01$ ). In the bone marrow derived from ShcC "knockout" mice in 3 passages, it is demonstrated the biphasic morphology in size. In cutaneous defects in ShcC "knockout" mice significantly delayed the wound healing. Therefore, ShcC may involve in cutaneous wound healing by mesenchymal stem or stromal cells.

## V 43-3

***The fate of human mesenchymal stem cells bone regeneration******T. Imaizumi<sup>1</sup>, K. Akino<sup>2</sup>, A. Hirano<sup>1</sup>, S. Akita<sup>1</sup>***<sup>1</sup>Nagasaki University, Department of Plastic Surgery, Nagasaki, Japan,<sup>2</sup>Nagasaki University, Department of Developmental and Reconstructive Medicine, Nagasaki, Japan

Bone marrow derived cells such as the human mesenchymal stem cells (hMSCs) successfully bone regenerated, however, there are little data on how and when the cells contribute to this event. As the hMSCs may be able to differentiate to mesenchymal lineage in each specific condition, further in vivo analysis is still lacking and the mechanisms are ambiguous. In order to elucidate the cell kinetics, proliferation and differentiation, the hMSCs-transfected with Green Fluorescent Protein (GFP) DNA plasmid, further kinetics were investigated. GFP-transfected hMSCs were grafted with gelatin sponge (Gelform) in the 5-mm full-thickness cranial bone defects of nude rats. The defects were healed in the grafted GFP-transfected hMSCs by 4 weeks post-operatively in accordance to the previous experiment, which was identical to that of without GFP-transfection but hMSCs grafting. Superficial layer, independent of the adjacent rat bone edge, at day 7 demonstrated the strong immunoreactivities of both GFP and osteocalcin, which indicates the matured bone, with the cell nuclear antigens of 6-Diamidino-phenylindole, Dihydrochloride (DAPI). In the same layer, polyomavirus enhancer binding protein 2 (PEBP 2) was also depicted as a core binding factor 1 (cbfa1), an osteogenic transcription factor expressed in some cells among the interstitial fibroblast-like cells along with GFP immunoreactivities. Taken together, PEBP 2 transcription was co-localized with osteocalcin expressions and these expressions were all strongly GFP immunoreactive. Therefore, the grafted hMSCs were located in independent of the pre-existing rat bones and osteogenesis is regulated transcriptionally via PEBP 2 and osteocalcin by autogenic regulation and the osteogenesis was enhanced with presence of osteogenic cytokines such as bone morphogenetic protein-2 (BMP-2) and basic fibroblast growth factor (bFGF).

## V 43-4

**Chronic wound fibroblasts: ageing before their time?**

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**Introduction:** Chronic non-healing wounds are a major health problem and affect 3 % of the population over 65 years of age. Age-related functional changes in dermal fibroblasts may contribute to this dysfunctional healing phenotype. The aim of this study was to investigate potential genotypic and phenotypic differences between patient-matched chronic wound fibroblasts (CWF) and normal skin fibroblasts (NF). In addition, we sought to investigate the role played by cellular and molecular ageing as a contributory factor in these wounds.

**Methods:** CWF and NF were established in culture (n = 4) and RNA was extracted for transcriptional profile analysis using Affymetrix microarrays after serum-starvation (to synchronise the cells in G<sub>0</sub>) and subsequent serum re-stimulation (to mimic a wound healing response). Phenotypic characteristics were also assessed throughout their proliferative lifespans including cellular proliferation (population doublings), senescence (cell morphology, senescence associated  $\beta$ -Galactosidase activity [SA  $\beta$ -Gal] and telomere length [using the novel PCR-based single telomere length analysis; STELA]), extracellular matrix reorganisation and ability to repopulate an experimental wound.

**Results:** Microarray analysis of CWF and NF following serum-stimulation demonstrated differential expression of 118 genes, including molecules involved in the protection against oxidative stress (e. g. glutaredoxin, oxidative stress responsive-1). In long-term culture CWF proliferated more slowly than NF and senesced at earlier time points (p < 0.01). The onset of premature senescence within the CWF populations significantly decreased their abilities to reorganise the surrounding extracellular environment (p < 0.01) and repopulate a wound. Premature senescence in CWF was confirmed by increased SA  $\beta$ -Gal staining and their larger, polygonal morphology. Analysis of telomere lengths in these samples revealed that replicative senescence was predominantly (3/4 samples) telomere-independent.

**Conclusions:** The results demonstrate that CWF have a genotype and phenotype distinct from patient-matched NF. The senescent phenotype of fibroblasts from some, but not all wounds, is independent of telomere shortening. One hypothesis that supports telomere-dependent and -independent mechanisms of cellular senescence involves differential levels of oxidative stress

within the wound environment. Elevated levels of stress could drive telomere-dependent senescence by stimulating cell turnover. However, extremely high levels of oxidative stress bypass the normal methods of telomere-dependent senescence causing direct DNA damage and subsequent cell senescence.

## V 43-5

**Wound-healing defect of CD18<sup>-/-</sup> mice due to a decrease in TGF $\beta$ ,1 and myofibroblast differentiation**

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The  $\beta$ 2 leukocyte integrins are heterodimers, composed of a common  $\alpha$  chain (CD18) and one out of four distinct  $\beta$  chains (CD11). They are pivotal for migration and signaling of hematopoietic cells during inflammatory processes and immune responses. Lack of functional  $\beta$ 2 integrin causes leukocyte-adhesion deficiency type 1 (LAD1), a life-threatening primary immunodeficiency syndrome with severe recurrent microbial infections, leukocytosis and impaired wound healing. Initial data revealed significantly increased wound sizes in a murine model for LAD1 (CD18<sup>-/-</sup>) from day 5 to 14 after application of full thickness wounds on mouse backs. We now addressed the question whether this impairment in wound healing was a consequence of reduced wound contraction potentially caused by disturbed myofibroblast recruitment. Therefore, we analyzed expression of markers critical for myofibroblast differentiation by immunohistochemistry and Western blotting. We found that both splice variant ED-A of fibronectin and  $\alpha$ -smooth muscle actin were substantially reduced in CD18<sup>-/-</sup> mice at day 5 and 7 after wounding, respectively, indicating impaired myofibroblast differentiation. Interestingly, TGF $\beta$ 1 and its receptor TGF $\beta$ -RII were also largely decreased. Since TGF $\beta$ 1 is a key factor for granulation tissue formation and promotes wound contraction, we supplemented TGF $\beta$ 1 by subcutaneously injecting two different doses (0.45  $\mu$ g, 0.1  $\mu$ g) into the wound margins at day 1, 3 and 5 after wounding of CD18<sup>-/-</sup> and wild-type mice. As a result, we observed a rescued wound closure in CD18<sup>-/-</sup>, similar to wild-type mice. Since in wounds of CD18<sup>-/-</sup> mice, defective migration leads to a severe reduction of neutrophils, we envisioned that infiltrating macrophages may not be able to phagocytose apoptotic CD18<sup>-/-</sup> neutrophils, thus, lacking their main stimulus to secrete TGF $\beta$ 1. We demonstrated that in the absence of neutrophils, or in co-cultures with CD18<sup>-/-</sup> neutrophils, TGF $\beta$ 1 release by macrophages was dramatically reduced due to defective phagocytic clearance of CD18<sup>-/-</sup> neutrophils, whereas pro-inflammatory cytokines were increased. Deviant from

former views, our data demonstrate that growth factors released by neutrophils in a paracrine fashion are important for wound contraction and healing. It remains to be seen whether CD18 is also involved in migration of myofibroblast precursors.

### V 43-6

#### ***Upregulation of lysyl hydroxylase 2 b in wound healing leads to altered collagen cross-linking***

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Hypertrophic scar formation in deep dermal wounds is associated with excessive collagen deposition and contraction. Besides increase collagen synthesis and decreased collagen degradation, the appearance of a different type of cross-linking, has been described in the literature in fibrosis of the skin. It was shown that collagen cross-linked by the hydroxyl-allysine route, the fibrotic type, is less assessable for degradation by MMP-1 than cross-links of the allysine route, the normal type of cross-linking in the skin. This type of cross-linking could therefore contribute to the process of collagen accumulation. Recently the key enzyme responsible for this type of cross-linking has been identified as lysyl hydroxylase type 2 (LH2 or PLOD2). This enzyme also influences fibril formation, overexpression of LH2 results in a decrease in fibril diameter. In this study we investigated the expression profile of LH2, collagen type I and III in time after wounding and determined the collagen cross-linking type of the scars in the experimental pig model. In pig full thickness wounds were created, the wounds were transplanted with a meshed (1:3) split skin autograft. At different time points after wounding biopsies were taken for evaluation. RNA levels were determined with real time RT-PCR. The type of cross-linking was determined in hydrolyzed samples by reverse-phase high performance liquid. The hydroxyl-allysine type crosslink in tissue samples from scars is significantly higher than in normal pig skin. The expression level of LH2 is increased in the wound during the first 3 weeks after wounding. Collagen type I and III expression are increased as well during this period. Pico Sirius red staining of the scar shows an altered architecture of the collagen fibres. In normal skin the collagen bundles are thicker and randomly orientated (basket weave pattern) whereas in the scar the bundles are thinner and aligned parallel to each other. The spatial and temporal increase of LH2 expression coincides with the elevated collagen type I and III expression. This results in increased deposition of collagen fibers of the fibrotic type, which is less susceptible for degradation by collagenase.