Chronic Venous Insufficiency
Chronic Venous Insufficiency

Has been recognized since ancient times

- By Greek physicians (Hippocrates 460-377 B.C.)
- By Roman physicians (centuries later)
- These disease entities continue to defy understanding
Common and progressive disorder

• found in many parts of the world
• a condition with ambulatory venous hypertension
• affects approximately 5% to 15% of the adult Population
• 1% develop venous ulcers
• CVI consumes 1-2% of the healthcare budget of the United States and European countries
• The term CVI is used to describe signs and symptoms of chronic venous hypertension in the lower limbs.

• This condition is generally considered as the pathophysiological trigger of skin changes, the most serious of which is ulceration.
• The clinical hallmark of CVI is distal venous hypertension, which follows the development of valvular incompetence, reflux, and/or venous obstruction.

• At the cellular level there is abnormal metabolism of the connective tissue matrix of the vein wall with a marked increase in fibrous tissue and abnormal deposition of collagen in both the vein wall and the skin.
Widmer’s Classification

It is based exclusively on objective signs

3 stages:

• 1. Corona phlebectatica paraplanteralis, edema
• 2. Trophic lesions (lipodermatosclerosis, atrophie blanche, dermatitis).
• 3. Active or healed leg ulcer
CVI-classifications

CEAP Classification
C: Clinical
E: Etiology
A: Anatomy
P: Pathophysiology
CEAP Classification

0 = No visible or palpable signs of venous disease
1 = Telangiectasia or reticular veins
2 = Varicose veins
3 = Edema
4 = Skin changes (pigmentation, venous eczema, lipodermatosclerosis)
5 = Skin changes as defined above with healed ulcer
6 = Skin changes as defined above with active ulceration
Clinical*  
\( C_0 \) - No clinical signs  
\( C_1 \) - Small varicose veins  
\( C_2 \) - Large varicose veins  
\( C_3 \) - Edema  
\( C_4 \) - Skin changes without ulceration  
\( C_5 \) - Skin changes with healed ulceration  
\( C_6 \) - Skin changes with active ulceration  

Etiology*  
\( E_C \) - Congenital  
\( E_P \) - Primary  
\( E_S \) - Secondary  
(usually due to prior DVT)  

Anatomy*  
\( A_S \) - Superficial veins  
\( A_D \) - Deep veins  
\( A_P \) - Perforating veins  

Pathophysiology*  
\( P_R \) - Reflux  
\( P_O \) - Obstruction  

“Early application of compression should be performed to correct swelling and progressive scarring and to initiate the healing process by improving the venous microcirculation.”  
Kistner R. Specific Steps to Effective Management of Venous Ulceration. Supplement to Wounds June 2010.  

First of these is venous microangiopathy. It evolves from distension of the capillary walls with subsequent leakage of macromolecules fibrinogen, into the dermis and subcutaneous tissue of the lower leg. Once in the extravascular space, fibrinogen polymerizes to form a pericapillary fibrin cuff that prevents the exchange of oxygen and nutrients leading to cell death and ulceration. The abnormal diffusion of macromolecules into the extracellular space traps growth factors and blood cells. The resulting vessel growth and deformity are associated with elongation, dilation, and tortuosity of capillary beds. Endothelial damage with widening interendothelial spaces increased pericapillary edema.
randomized clinical trials

1) bioengineered tissue
2) surgery
3) electrical stimulation

compared with standard of care regardless if treatment group was combined with compression.
Compression Therapy

• Compression stockings are the criterion standard treatment for venous and lymphatic disorders
• Compression aims to reduce or control venous reflux and peripheral edema
• Venous compression may achieve narrowing of veins, restoration of valvular competence, or acceleration of venous flow
Pathological process is incompetent valves within the veins themselves

valves are incompetent
blood is allowed to flow in a retrograde
disruption of Starling equilibrium
net loss of fluids into surrounding tissue
accumulated fluid inactivates the fatty acid of dermal sebumskin
vulnerable to breakdown and subsequent infection from common
dermal pathogens - streptococci and staphylococci
Skin Changes at CVI

- Gravitational dermatitis
- Hyperpigmentation
- Lipodermatosclerosis
- Their presence mirrors microcirculatory disorders
  - induration
  - pigmentation
  - inflammation
• Venous ulcers are approximately 80% of all leg ulcerations and they are also known to have the highest recurring rates.

• Venous ulcers are not generally as painful, do not lead to amputation, do not require surgical intervention as often as ulcers caused by arterial insufficiency.
Venous ulcers are usually located over the medial malleolus where the long saphenous vein is more superficial and the pressure is greatest.
Trauma or infection may localize ulcers more proximal or laterally. Ulcers above the mid calf or on the foot commonly suggest another cause.
Venous ulcers are shallow, they generally have borders with irregular margins that are either flat or with a slight steep elevation. The ulcer bed is covered initially by yellow fibrinous slough.

Healing is very slow, often from months to years.
Venous Ulcer

Differential Diagnosis

Neoplastic leg ulcers:

• Basal cell carcinoma
• Squamous cell carcinoma
• Malignant melanoma
Compression Therapy

• Compression stockings are the criterion standard treatment for venous and lymphatic disorders

• Compression aims to reduce or control venous reflux and peripheral edema

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Surgery

• Surgical intervention for venous ulceration focuses on ablating the pathologic veins
• Surgical treatment addresses the underlying venous pathology of VLU
Bioengineered Tissue

- noninfected, chronic, and partial- and full-thickness chronic VLUs
The primary aims of graduated compression management (from the toes to the knee) are:

- to reduce the pressure on the superficial venous system
- to aid venous return of blood to the heart
- to discourage edema by reducing the pressure difference between the capillaries and the tissues
### BIOENGINEERED TISSUE FOR HEALING AND PREVENTION OF VLU

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Study Design</th>
<th>Duration of Study and Follow-up</th>
<th>Population</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Falanga et al.²²</td>
<td>Allogeneic cultured human skin equivalent (Apligraf; Organogenesis)</td>
<td>Maximum of 5 times in first 3 wk</td>
<td>Healing: 6 mo Follow-up: 12 mo</td>
<td>Treatment n = 146; Compression n = 129</td>
<td>Wound healing: bioengineered tissue (63%) vs compression (43%) (P &lt; .02); Wound area reduction: NS; Recurrence: bioengineered tissue (12%) vs compression (18%) (P &gt; .05); Adverse events: death (5 bioengineered tissue and 4 control), adverse experience (3 bioengineered tissue and 7 control), wound infection (2 bioengineered tissue), and cellulitis (12 bioengineered tissue and 10 control)</td>
</tr>
<tr>
<td>Gondko et al.²⁵²⁶</td>
<td>Alllogeneic growth-amplified, human keratinocytes and fibroblasts spray (SB Pharmaceuticals Inc, Fort Worth, Texas)</td>
<td>Weekly for 12 wk</td>
<td>Healing: 3 mo Follow-up: 6 mo</td>
<td>2.5/1.9² n = 14; 5/1.9² n = 17; 10/1.9² n = 15; 2.5/1.19² n = 17; 5/1.19² n = 16; 10/1.19² n = 16</td>
<td>Wound healing: bioengineered tissue (40%) vs compression (33%) (P &gt; .05); Wound area reduction: NS; Recurrence: bioengineered tissue (61%) vs compression (52%) (P &gt; .05); Adverse events: NS</td>
</tr>
<tr>
<td>Harding et al.²⁰²¹⁵²⁷</td>
<td>Human allogeneic fibroblast-derived dermal tissue (Dermagraft)</td>
<td>4 applications over 12 wk</td>
<td>Healing: 3 mo Follow-up: 6 mo</td>
<td>Compression n = 15; Treatment n = 186; Compression n = 180</td>
<td>Wound healing: bioengineered tissue (34%) vs compression (21%) (P = .2); Wound area reduction: bioengineered tissue (83.7%) vs compression (75.0%) (P &gt; .05)</td>
</tr>
<tr>
<td>Krishnamoorthy et al.²⁰²³²⁴</td>
<td>Allogeneic fibroblast-derived dermal sheet (Dermagraft)</td>
<td>Span of 12 wk</td>
<td>Healing: 3 mo</td>
<td>Group 1 (n = 13): 12 applications; Group 2 (n = 13): 14 applications; Group 3 (n = 14): 1 application</td>
<td>Wound healing: group 1 (38%), group 2 (38%), group 3 (7%) vs compression (15%) (P &gt; .05); Wound area reduction: NS; Recurrence: NS; Adverse events: NS</td>
</tr>
<tr>
<td>Lindgren et al.²⁰²⁷²⁸</td>
<td>Allogeneic keratinocyte sheets</td>
<td>Weekly for 12 wk</td>
<td>Healing: 2 mo</td>
<td>Compression n = 15; Treatment n = 12</td>
<td>Wound healing: bioengineered tissue (13%) vs compression (17%) (P &gt; .05); Wound area reduction: bioengineered tissue (35%) vs compression (15%) (P &gt; .05); Recurrence: NS; Adverse events: NS</td>
</tr>
<tr>
<td>Omar et al.²⁰²⁰²⁹</td>
<td>Allogeneic fibroblast-derived dermal sheet (Dermagraft)</td>
<td>4 applications in 12 wk</td>
<td>Healing: 3 mo</td>
<td>Treatment n = 10; Compression n = 8</td>
<td>Wound healing: bioengineered tissue (50%) vs compression (13%) (P &gt; .05); Wound area reduction: bioengineered tissue (84%) vs compression (16%) (P = 0.02); Recurrence: NS; Adverse events: Wound infection (4 bioengineered tissue and 3 control), osteomyelitis (1 bioengineered tissue), and noncompliance (1 control); Wound healing: bioengineered tissue (41%) vs compression (35%) (P &gt; .05); Wound area reduction: NS; Recurrence: 13% bioengineered tissue vs 14% compression P &gt; .05; Adverse events: NS</td>
</tr>
<tr>
<td>Tepe et al.²¹</td>
<td>Allograft cultured epidermal</td>
<td>Weekly for 6 wk</td>
<td>Healing: 6 wk Recurrence: 6 mo</td>
<td>Treatment n = 22; Compression n = 21</td>
<td>Wound healing: bioengineered tissue (13%) vs compression (14%) (P &gt; .05); Adverse events: NS</td>
</tr>
</tbody>
</table>

*Cell concentration (SP cells/ml) (SP ratio: keratinocyte:fibroblast)
|Abbreviation: NS, not significant
### ELECTRICAL STIMULATION FOR HEALING AND PREVENTION OF VLUS

<table>
<thead>
<tr>
<th>Study</th>
<th>Ulcer Type</th>
<th>Duration and Frequency</th>
<th>Current Parameters</th>
<th>Treatment</th>
<th>Wound Healing</th>
<th>Wound Area Reduction</th>
<th>Adverse Events</th>
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<tr>
<td>Franek et al., 2000</td>
<td>Venous ulcers using FREMS</td>
<td>50 min, daily, 6 d a week for 3 wk</td>
<td>100 V, 0.1 ms, 100 Hz</td>
<td>Treatment n = 33</td>
<td>Wound healing: NS</td>
<td>Wound area reduction: ES 59%, ointment 35% vs control 25% (P &lt; .05)</td>
<td>Adverse events: no events</td>
</tr>
<tr>
<td>Still et al., 1992</td>
<td>Venous ulcers using PEMF</td>
<td>3 hours, daily, 7 d a week for 2 mo</td>
<td>0.06 mV/cm. The signal is 3-part pulse (+, −, +) of 3.5-ms width</td>
<td>Treatment n = 18</td>
<td>Wound healing: NS</td>
<td>Wound area reduction ES 48% vs control increase of 42% (P &lt; .0002)</td>
<td>Adverse event: no events</td>
</tr>
<tr>
<td>Ogrin et al., 2009</td>
<td>Venous ulcers using transcutaneous electrical nerve stimulation</td>
<td>5 min, twice a day for 3 mo</td>
<td>4 mA, 5Hz</td>
<td>Treatment n = 13</td>
<td>Wound healing: ES 57% vs placebo 67% (P &gt; .05)</td>
<td>Wound area reduction: ES 0.8 ± 0.2 cm² vs placebo 0.7 ± 0.2 cm² per week (P &gt; .05)</td>
<td>Adverse event: NS</td>
</tr>
<tr>
<td>Lundberg et al., 1992</td>
<td>VLUs in diabetics using alternating current</td>
<td>20 min, twice a day for 3 mo</td>
<td>80 Hz, pulse width 1 ms</td>
<td>Treatment n = 14</td>
<td>Wound healing: ES 42% vs 15% placebo (P &lt; .05)</td>
<td>Wound area reduction: 59 ± 11% ES vs 39 ± 14% placebo (P &lt; .05)</td>
<td>Adverse event: allergy (2 ES and 1 placebo), pain (3 ES, and 2 placebos), and refusal/ nonattendance (3 ES and 2 placebos)</td>
</tr>
</tbody>
</table>

**Abbreviations:** NS, not significant; PEMF, pulsed electromagnetic field; FREMS, frequency-modulated electromagnetic neural stimulation

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# SURGICAL TREATMENT FOR HEALING AND PREVENTATION OF VLUs

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment of Interest</th>
<th>Duration of Study and Follow-up</th>
<th>Population</th>
<th>Outcome</th>
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<tr>
<td>Gohel et al., [46] 2007</td>
<td>Saphenofemoral junction disconnection, stripping of the long saphenous vein to below the knee, and calf varicosity avulsions</td>
<td>Healing rates at 3 y Recurrence rates at 4 y</td>
<td>Treatment n = 258 Compression n = 242</td>
<td>Wound healing: surgery (93%) vs compression (89%) (P = .73) Wound area reduction: NS Reocurrence: surgery (31%) vs compression (56%) (P &lt; .01) Adverse events: 2 compression patients admitted for cellulitis, 8 postoperative complications (1 deep vein thrombosis, 5 wound infections, 1 hematoma, 1 phlebitis) Wound healing: surgery (68%) vs compression (64%) (P = .75) Wound area reduction: NS Recurrence: NS Adverse events: 2 compression and 1 surgery patients were treated for cellulitis Wound healing: surgery (72%) vs compression (53%) (P = .11) Wound area reduction: NS Recurrence: surgery (22%) vs compression (23%) (P &gt; .05) Adverse events: NS Wound healing: surgery (100%) vs compression (96%) (P &gt; .05) Wound area reduction: NS Reocurrence: surgery (9%) vs compression (38%) (P &lt; .05) Adverse events: NS</td>
</tr>
<tr>
<td>Guest et al., [45] 2003</td>
<td>Superficial venous surgery</td>
<td>18 mo</td>
<td>Treatment n = 37 Compression n = 39</td>
<td>Wound healing: surgery (68%) vs compression (64%) (P = .75) Wound area reduction: NS Recurrence: NS Adverse events: 2 compression and 1 surgery patients were treated for cellulitis Wound healing: surgery (72%) vs compression (53%) (P = .11) Wound area reduction: NS Recurrence: surgery (22%) vs compression (23%) (P &gt; .05) Adverse events: NS</td>
</tr>
<tr>
<td>van Gent et al., [44] 2006</td>
<td>Subfascial endoscopic perforating vein surgery combined with superficial vein ligation</td>
<td>3 y</td>
<td>Treatment n = 97 Compression n = 103</td>
<td>Wound healing: surgery (68%) vs compression (64%) (P = .75) Wound area reduction: NS Recurrence: surgery (22%) vs compression (23%) (P &gt; .05) Adverse events: NS</td>
</tr>
<tr>
<td>Zamboni et al., [43] 2003</td>
<td>Minimally invasive surgical hemodynamic correction of reflux</td>
<td>3 y</td>
<td>Treatment n = 21 Compression n = 24</td>
<td>Wound healing: surgery (68%) vs compression (64%) (P = .75) Wound area reduction: NS Recurrence: surgery (22%) vs compression (23%) (P &gt; .05) Adverse events: NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant
POOR PROGNOSTIC INDICATORS

For venous ulcer healing are:
• large size
• long duration history of venous ligation
• ABI of less than 0.8
• presence of fibrin on more than 50% of the ulcer surface
If the ulcer fails to heal, the diagnosis has to be reevaluated and the following additional investigations should be done:

- Biopsy
- Autoimmune screen
- Blood sugar level
- X-ray
“Once an ulcer patient always a potential ulcer patient”

Recurrence rates of venous ulcers after treatment are high. Once the patient’s ulcer is healed, careful skin care, continuous vigilance and strict use of compression therapy must be emphasized.
Conclusions

• Compression therapy may be the criterion standard in treatment of VLUs, the results are less than ideal.
• Healing is low, and the rate of recurrence is high.
• Little evidence to support the use of adjunctive electrical stimulation and Bioengineered tissue studies were very small.
• Surgical treatment studies reported produced a higher percentage of healed wounds, as well as the lowest recurrence rates. Surgery patients are probably healthier patients with venous disease that is amenable to surgical repair. High-risk patients and patients with severe venous disease were appropriately excluded.

One of the key benefits of surgical treatment is the apparent reduction in ulcer recurrence. Small sample size, electrical stimulation showed positive results and promise.