Endothelial dysfunction
Venous insufficiency and varices

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Endothelium

• A type of epithelium that lines the interior surface of blood vessels and lymphatic vessels
• Single layer of squamous endothelial cells with tight junctions
Continuous

- Basement membrane
- Endothelial layer (tunica intima)
- Intercellular cleft

Fenestrated

- Fenestrations

Sinusoid

- Incomplete basement membrane
- Intercellular gap
Figure 1. Endothelium and permeability.

A Capillary

Continuous Non-fenestrated

Lumen

TEC (transendothelial) channel

H₂O small solutes

Intercellular cleft

Tracer

Skin

Lung

Heart

Continuous fenestrated

Diaphragm

H₂O small solutes

Tracer

Endocrine glands
GI mucosa
Glomerulus

Discontinuous/sinusoidal

Sinusoidal fenestrae/Gaps

H₂O small solutes

Tracer

Liver

Clathrin-coated pit

Recycling
Early
Sorting
Lysosome

B Post-capillary venule

Lumen

VVO

Intercellular cleft

Caveolae opening into cleft

Widening of intercellular cleft

Fluids and solutes

William C. Aird Circ Res. 2007;100:158-173
Endothelial cell

- Large amounts of **vesicles** and **caveolae** along the luminal surface - transendothelial **transport** of biologically active substances
Endothelium

• Mesodermal origin
• EC are aligned and elongated in direction of flow
• EC line the *entire circulatory system* – one of the largest organ systems
• Unique functions
Endothelium

• Fluid filtration (glomeruli)
• Barrier function
• Blood vessel tone (vasodilation and vasoconstriction)
• Hemostasis
• Hormone trafficking
• Inflammation - neutrophil recruitment
• Angiogenesis
• Secretion of mediators – normal vascular function
Barrier function

FIGURE 4 | Scheme of a protein structure of endothelial intercellular junctions (EIJs).
Release of vascular dilators
NO
Prostaglandins

Release of vascular constrictors
Angiotensin II
Endothelin I

Release of antithrombotic factors
Plasminogen activator
Thrombomodulin
Heparan

Release of prothrombotic factors
vWF
Plasminogen inhibitor

Transendothelial migration of leukocytes

Suppression of release of proinflammatory mediators and ROS

FIGURE 2 | Endothelial function in the norm. Arterial endothelial cells are involved in the maintenance of vascular homeostasis by providing balanced release of vasodilatating/vasoconstricting factors and prothrombotic/antithrombotic substances that inhibits the endothelial adhesion of leukocytes and thus, prevents the initiation of vascular inflammation.
Figure 2. Endothelium and leukocyte trafficking.

Arteriole | Capillary | Venule
---|---|---
**A** | | 
 BASEMENT MEMBRANE

**B** | | 
 Adhesion | Transmigration
 ICAM-1

**C** | | 
 Adhesion | Transmigration
 ICAM-1

**D** | | 
 Discontinuous basement membrane
 Space of Disse

Skin, Muscle, Mesentery
Lung
Liver
Mesenteric lymph node

William C. Aird Circ Res. 2007;100:158-173
FIGURE 3 | Penetration of a blood cell through the endothelium into the arterial intima. Scanning electron microscopy (SEM). Scale bar = 5 μm. Image is adapted from Bobryshev (1983).
Figure 4. Mechanisms of EC heterogeneity.
Endothelial dysfunction

• Systemic pathological state of the endothelium
• **Imbalance** between vasodilating and vasoconstricting substances produced by the endothelium
• Shift of the balance in favour of **vasoconstrictive**, **pro-inflammatory** and **pro-thrombotic** effects
• Mainly due to reduced bioavailability and bioactivity of **nitric oxide (NO)**
Vasodilation

• Nitric oxide
• EDHF
• Prostacyclin

• Acetylcholine
• Bradykinin
Nitric oxide

• Most abundant free radical in the body
• Halflife of NO is affected by its chemical reaction and inactivation by superoxide anion
• $\cdot O_2^- + \cdot NO \rightarrow ONOO^-$
Shear stress

• NO is released after **shear stress** in the vessel – vasodilation
• NO mediated vasodilation decreases shear stress
• If shear stress is chronic – upregulation of inflammatory cytokines – endothelial dysfunction
Protective effects of NO

• Smooth muscle relaxation and vasodilation
• Lowering blood pressure
• Reducing proliferation of vascular smooth muscle
• Inhibition of platelet aggregation
• Inhibition of expression of VCAM and ICAM
Vasoconstriction

- Endothelin-1
- Prostaglandin $H_2$
- Thromboxane $A_2$
- ROS
- Endothelium-bound ACE – angiotensin II
Regulatory Functions of the Endothelium

**Normal**
- Vasodilation: NO, PGI2, EDHF, BK, C-NP
- Thrombolysis: tPA, Protein C, TF-I, vWF
- Platelet Disaggregation: NO, PGI2
- Antiproliferation: NO, PGI2, TGF-β, Hep
- Lipolysis: LPL

**Dysfunction**
- Vasoconstriction: ROS, ET-1, TxA2, A-II, PGH2
- Thrombosis: PAI-1, TF-α, Tx-A2
- Adhesion Molecules: CAMs, P,E Selectins
- Growth Factors: ET-1, A-II, PDGF, ILGF, ILs
- Inflammation: ROS, NF-κB

Vogel R
The endothelium maintains vascular health

- Dilatation
- Growth inhibition
- Antithrombotic
- Anti-inflammatory
- Antioxidant

- Constriction
- Growth promotion
- Prothrombotic
- Proinflammatory
- Pro-oxidant
What causes Endothelial Dysfunction?

Negatively Affect:
- Smoking
- Diabetes
- High Blood Pressure
- High Cholesterol
- Weight Gain
- Mental Stress
- Excessive Inflammation

Positively Affect:
- Exercise
- Weight Loss
- Stress Reduction
- Cholesterol-Lowering Drugs
Consequences of ED

- Progenitor of atherosclerosis (ED is present long before onset of symptoms)
- Predictor of future cardiovascular events
Oxidative stress

- **Imbalance** between production of reactive oxygen species and ability of the system to detoxify the reactive intermediates or to repair the damage

- Key mechanism of endothelial dysfunction

- OS + ED are major factors for atherosclerosis
Oxidative stress

Endothelial dysfunction
Reduced NO bioavailability

Leukocyte adhesion & inflammation
Lipid deposition
Vascular smooth muscle cell proliferation

Platelet aggregation & thrombosis
Vasoconstriction

Progression of atherosclerosis and cardiovascular disease
LDL-specific antioxidant action

Native LDL

Vessel lumen

Endothelial cells

Vessel wall

Antioxidants impair cellular capacity to oxidize LDL

Antioxidants limit cellular responses to oxidized LDL

Oxidants

Vascular cells

Oxidized LDL

Cellular responses to oxidized LDL

†Monocyte adhesion
†Foam-cell formation
†Cytotoxicity
†Vascular dysfunction

Formation and activation of atherosclerotic lesions
SOD = Superoxide Dismutase
CAT = Catalase
GP = Glutathione Peroxidase
GR = Glutathione Reductase
L-Arg = L-Arginine
L-Cit = L-Citrulline
ONOO⁻ = Peroxynitrite
•ON = Nitric Oxide
O₂⁻ = Superoxide
H₂O₂ = Hydrogen Peroxide
H₂O = Water
GSSG = Glutathione Disulfide
ED in disease

- Cardiovascular disease
- Diabetes
- Transplant vasculopathy
- Autoimmune diseases
- Celiac disease and irritable bowel syndrome
- Hematologic disorders
- Neurocognitive disorders
- Cirrhosis
1. ED in diabetes

- T1DM, T2DM
- Pathogenesis unclear
- Multifactorial etiology of ED
- 1. Insulin resistance
- 2. Pro-inflammatory signalling
- 3. Oxidative stress
- 4. Protein kinase C
- 5. Hyperglycemia
Figure 3. Pathogenesis and consequences of endothelial dysfunction in type 2 diabetes mellitus. Oxidative stress contributes to endothelial dysfunction by activating protein kinase C, polyol, hexosamine, and NF kappa B pathways, as well as increasing asymmetric dimethylarginine and advanced glycation end-products [4].
Insulin resistance in ED

- Insulin activates vasoprotective pathways
  - PI3K/Akt – eNOS expression and activation
- In contrast, MAPK/ERK pathway promotes ET-1 and cellular proliferation
- **In physiological conditions** – PI3K predominates
- **Insulin resistance** – PI3K deficiency, MAPK predominates – proatherogenic signalling
Pro-inflammatory signalling in ED

- Adipose tissue produces inflammatory cytokines
- TNFalpha, free fatty acids, RAGE activate NFkB that further stimulates expression of inflammatory genes
- Reduction of NO expression

Table 1. Inflammatory components of diabetes complications.

<table>
<thead>
<tr>
<th>Inflammatory cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukins IL-1, IL-6, IL-18</td>
</tr>
<tr>
<td>Tumour necrosis factor-alpha (TNF-α)</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adhesion molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercellular adhesion molecule 1 (ICAM-1)</td>
</tr>
<tr>
<td>Vascular cell adhesion molecule-1 (VCAM1)</td>
</tr>
<tr>
<td>E-selectin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCL-2 (MCP-1)</td>
</tr>
<tr>
<td>CX3CL1 (fractalkine)</td>
</tr>
<tr>
<td>CCL5 (RANTES)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transcription factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFkB</td>
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<table>
<thead>
<tr>
<th>Toll-like receptors</th>
</tr>
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<tbody>
<tr>
<td>TLR2</td>
</tr>
<tr>
<td>TLR4</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Profibrotic cytokines</th>
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</thead>
<tbody>
<tr>
<td>Transforming growth factor beta (TGF-β)</td>
</tr>
<tr>
<td>Connective tissue growth factor (CTGF)</td>
</tr>
</tbody>
</table>
Oxidative stress in ED

- OS as a unifying mechanism of endothelial injury
- OS leads to **diminished NO bioavailability**
  - Direct degradation of NO
  - Alterations in functional capacity of eNOS
Protein kinase C in ED

- PKCbeta is endothelial isoform of serin/threonine kinase
- Main contributor to ED observed in diabetes
- High FFA and glucose – high DAG (de novo from glucose) – activation of PKCbeta – induction of downstream events:
  - ET-1
  - VCAM
  - ICAM
  - NADPH oxidase
  - NFkB
  - Inhibition of PI3K and eNOS
Hyperglycemia in ED

• 1. PKC activation
• 2. Activation of hexosamine pathway – PKC
• 3. Activation of polyol pathway – PKC
• 4. Formation of advanced glycation end-products

• Unifying mechanisms is ROS overproduction
2. ED in hypertension

• ED as an early event in pathophysiology of essential hypertension that contributes to subclinical target organ damage and progression of atherosclerosis
  • Defective endothelial L-arginine/NO pathway
  • Impaired responsiveness to exogenous NO
  • Reduced generation of platelet NO
  • In the presence of oxidative stress
• Pro-inflammatory, pro-atherosclerotic, pro-thrombotic phenotype
Mechanism of ED in hypertension

- Hypertension as **cause** rather than consequence of endothelial dysfunction
- Hypertension-induced oxidative stress
Measuring endothelial function

- 1950s – endothelium as a dynamic organ with diverse capabilities
- Invasive methods
- 1992 – Celermajer et al. proposed first non-invasive method for assessment of endothelial function - diameter of superficial femoral and brachial arteries
  - At rest
  - During reactive hyperemia (endothelium-dependent dilatation)
  - After sublingual nitroglycerin (endothelium-independent dilatation)
Table 4. Criteria for an Optimal Endothelial Function Test

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflects disease state</td>
</tr>
<tr>
<td>Reversible with interventions</td>
</tr>
<tr>
<td>Mirrors coronary endothelial function</td>
</tr>
<tr>
<td>Improves risk stratification</td>
</tr>
<tr>
<td>Reproducible</td>
</tr>
<tr>
<td>Operator independent</td>
</tr>
<tr>
<td>Noninvasive (no or low risk for the patient)</td>
</tr>
<tr>
<td>Ease of use</td>
</tr>
<tr>
<td>Inexpensive</td>
</tr>
</tbody>
</table>
Vascular markers of ED

• Quantitative coronary angiography
• MRI
• PET
• Invasive measurement of forearm blood flow (FBF) by venous occlusion plethysmography
Vascular markers of ED

- Non-invasive measurement
  - **Flow-mediated dilation (FMD)** – macrovascular function
  - Peripheral arterial tonometry – microvascular function
  - Laser Doppler flowmetry
<table>
<thead>
<tr>
<th>Technique</th>
<th>Vascular Bed</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Stimulus (Examples)</th>
</tr>
</thead>
</table>
| Coronary epicardial vasoreactivity (QCA)     | Epicardial macrovascular conduit arteries | Assessment directly in the coronary vascular bed  
Cold standard                                                                                      | Invasive  
Expensive  
Time intensive  
Limited to those undergoing coronary angiography  
Challenging for serial measurements                                                                 | Ach  
Exercise  
Pacing  
CPT                                                                                                  |
| Coronary microvascular function–Doppler wires | Coronary microvascular resistance arteries | Assessment directly in the coronary microvasculature                          | Invasive  
Expensive  
Time intensive  
Limited to those undergoing coronary angiography  
Challenging for serial measurements                                                                 | Ach  
Adenosine  
Papaverine                                                                  |
| FMD                                           | Brachial artery  
Conduit artery | Easy access  
Correlation with invasive epicardial vascular function  
Many outcome studies  
Inexpensive  
Possibility to assess other important parameters (flow, baseline arterial diameters, FMC) | Challenging to perform well  
Disparate protocols for performance and standardizations  
Need for standardization                                                                 | Reactive Hyperemia  
Ach and other vasoactive substances                                                                 |
| Venous occlusion plethysmography              | Forearm vasculature  
Microvasculature | Easy access  
Vasoactive substances infused to generate a dose-response relationship  
Contralateral arm as a control                                                                 | Invasive (cannulation of the brachial artery)  
Time consuming                                                                                 | Ach and other vasoactive substances                                                                 |
| EndoPAT                                       | Finger  
Microvasculature | Easy to access and perform Automated  
Low interobserver and intraobserver variability  
Correlation with invasive microvascular vascular function | Expense of disposable finger probes  
PAT signal influenced by variable non endothelial factors                                           | Reactive hyperemia                                                  |

QCA indicates quantitative coronary angiography; Ach, acetylcholine; CPT, cold pressor test; FMD, flow-mediated dilation; FMC, flow-mediated constriction; and PAT, peripheral arterial tonometry.
Table 3. Technical Considerations in Flow-Mediated Dilation Measurements

<table>
<thead>
<tr>
<th>Subject preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting state (&gt;6 h)</td>
</tr>
<tr>
<td>No smoking or any tobacco consumption at least 6 h before study</td>
</tr>
<tr>
<td>No exercise or food/beverages that contain alcohol or caffeine or are rich in polyphenols (cocoa, tea, fruit juices) for &gt;12 h</td>
</tr>
<tr>
<td>No vitamins for at least 72 h</td>
</tr>
<tr>
<td>Vasoactive medications withheld on the morning of the study if possible with careful noting of the use and timing of any drugs</td>
</tr>
<tr>
<td>No exercise &gt;12 h before test</td>
</tr>
<tr>
<td>Quiet, temperature-controlled room</td>
</tr>
<tr>
<td>In female patients, repetitive studies should be made at the same time of the menstrual cycle (ideally on days 1–7 of the menstrual cycle)</td>
</tr>
<tr>
<td>Rest for at least 10 min before measurements</td>
</tr>
<tr>
<td>Supine position</td>
</tr>
<tr>
<td>Arm resting comfortable with cradle support with the imaged artery at the heart level</td>
</tr>
<tr>
<td>Test should be performed at the same time of the day (especially if multiple tests are performed)</td>
</tr>
<tr>
<td>Sphygmomanometer probe position and cuff occlusion time</td>
</tr>
<tr>
<td>Placement of the cuff 1–2 cm distal to the elbow crease</td>
</tr>
<tr>
<td>Other sites are discouraged because proximal cuff positioning affects the magnitude of the peak vasodilatory response</td>
</tr>
<tr>
<td>Occlusion time, 5 min (shorter inflation attenuates FMD response)</td>
</tr>
<tr>
<td>Cuff inflation to at least 50 mm Hg above systolic pressure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial artery with a minimum diameter (usually &gt;2 mm); small arteries are difficult to measure, and changes in absolute diameter correspond to big relative changes</td>
</tr>
<tr>
<td>If repetitive measurements are planned, site has to be replicated; anatomic landmarks should be used</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Image acquisition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal images obtained by high-resolution ultrasound (7.5–12 MHz)</td>
</tr>
<tr>
<td>A clear interface between the near and far arterial wall should be achieved</td>
</tr>
<tr>
<td>Diameter measurements are obtained in end diastole or averaged over the heart cycle</td>
</tr>
<tr>
<td>Stereotactic adjustable prop holding is essential to ensure image quality</td>
</tr>
<tr>
<td>Recording of the baseline diameter for at least 1 min</td>
</tr>
<tr>
<td>Simultaneous acquisition of pulse-wave Doppler velocity signals for quantification of shear stress (stimulus) if feasible; insonation angle should be &lt;60°</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automated edge detection should be used</td>
</tr>
<tr>
<td>Reported as maximal percentage change from baseline diameter (most reproducible)</td>
</tr>
<tr>
<td>Baseline diameter and absolute change reported also</td>
</tr>
<tr>
<td>Characterization of the hyperemic stimulus (ideally the flow-velocity time integral)</td>
</tr>
</tbody>
</table>
Biomarkers of ED

• **Assymetrical dimethylarginine ADMA** – endogenous competitive inhibitor of NO
• Oxidized LDL
• Endothelial microparticles
• Endothelial progenitor cells
• Endothelial glycocalyx
### Table 1. Methods of assessing endothelial function

<table>
<thead>
<tr>
<th>Coronary circulation</th>
<th>Peripheral circulation</th>
<th>Circulating biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>QCA</td>
<td>Ultrasonography: FMD</td>
<td>ADMA, NO</td>
</tr>
<tr>
<td>PET</td>
<td>Plethysmography: FABF</td>
<td>ET-1</td>
</tr>
<tr>
<td>MRI</td>
<td>Endo-PAT</td>
<td>hs-CRP</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td>vWF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PAI-1</td>
</tr>
<tr>
<td><strong>Vasodilatory stimuli</strong></td>
<td></td>
<td>ICAM, VCAM</td>
</tr>
<tr>
<td>Acetycholine</td>
<td></td>
<td>Selectins</td>
</tr>
<tr>
<td>Shear stress</td>
<td></td>
<td>EP cells</td>
</tr>
<tr>
<td>Nitrates</td>
<td></td>
<td>EMPs</td>
</tr>
<tr>
<td>NOS inhibitors</td>
<td></td>
<td>SNP s</td>
</tr>
</tbody>
</table>

**Legend:** QCA - quantitative coronary angiography, PET - positron emission tomography, MRI - magnetic resonance imaging, FMD - flow-mediated dilation, FABF - forearm blood flow, Endo-PAT - non-invasive peripheral artery tonometry, NOS - nitric oxide synthase, ADMA - asymmetric dimethylarginine, NO - nitric oxide, ET-1 - endothelin-1, hs-CRP - high-sensitivity C-reactive protein, vWF - von Willebrand factor, PAI-1 - plasminogen activator inhibitor 1, ICAM - intercellular adhesion molecule, VCAM - vascular cell adhesion molecule, EP cells - endothelial progenitor cell, EMP - endothelial-derived microparticle, SNP - single nucleotide polymorphisms.
ED in periodontitis

Treatment of Periodontitis and Endothelial Function

Maurizio S. Tonetti, D.M.D., Ph.D., Francesco D’Aiuto, D.M.D., Ph.D.,
Luigi Nibali, D.M.D., Ph.D., Ann Donald, Clare Storry, B.Sc.,
Mohamed Parkar, M.Phil., Jean Suvan, M.Sc., Aroon D. Hingorani, Ph.D.,
Patrick Vallance, M.D., and John Deanfield, M.B., B.Chir.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control-Treatment Group (N=59)</th>
<th>Intensive-Treatment Group (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>47.8±6.3</td>
<td>47.7±7.9</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>30 (51)</td>
<td>30 (49)</td>
</tr>
<tr>
<td>Smoking status — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>21 (36)</td>
<td>24 (39)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>18 (31)</td>
<td>19 (31)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20 (34)</td>
<td>18 (30)</td>
</tr>
<tr>
<td>Family history of cardiovascular disease — no. (%)</td>
<td>40 (68)</td>
<td>38 (62)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>41 (69)</td>
<td>41 (68)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (10)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (17)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Body-mass index‡</td>
<td>27.3±5.4</td>
<td>27.2±5.0</td>
</tr>
<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124.5±17.4</td>
<td>125.6±15.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.2±11.1</td>
<td>80.5±11.4</td>
</tr>
<tr>
<td>Brachial-artery diameter — mm</td>
<td>3.6±0.6</td>
<td>3.7±0.8</td>
</tr>
<tr>
<td>Reactive hyperemia ratio§</td>
<td>8.9±4.1</td>
<td>8.8±4.2</td>
</tr>
<tr>
<td>Flow-mediated dilatation — %</td>
<td>6.5±2.6</td>
<td>7.1±4.2</td>
</tr>
<tr>
<td>Nitroglycerin-mediated dilatation — %¶</td>
<td>17.9±6.9</td>
<td>17.9±6.5</td>
</tr>
<tr>
<td>CRP — mg/liter</td>
<td>3.8±3.3</td>
<td>2.5±2.7</td>
</tr>
<tr>
<td>Interleukin-6 — pg/ml</td>
<td>2.1±3.9</td>
<td>2.4±5.4</td>
</tr>
<tr>
<td>Soluble E-selectin — ng/ml</td>
<td>20.3±13.6</td>
<td>19.6±14.0</td>
</tr>
<tr>
<td>t-PA — ng/ml</td>
<td>4.5±0.6</td>
<td>3.2±0.4</td>
</tr>
<tr>
<td>PAI-1 — ng/ml</td>
<td>21.39±1.8</td>
<td>21.5±1.5</td>
</tr>
<tr>
<td>Von Willebrand factor — IU/ml</td>
<td>0.87±0.16</td>
<td>0.90±0.19</td>
</tr>
<tr>
<td>Leukocyte count — ×10^9/liter</td>
<td>7.1±2.0</td>
<td>6.4±1.6</td>
</tr>
<tr>
<td>Cholesterol — mmol/liter</td>
<td>5.3±1.2</td>
<td>5.3±1.0</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>1.5±0.4</td>
<td>1.5±0.4</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>3.2±1.0</td>
<td>3.1±0.9</td>
</tr>
<tr>
<td>Glucose — mmol/liter</td>
<td>5.1±0.6</td>
<td>5.1±0.8</td>
</tr>
<tr>
<td>Triglycerides — mmol/liter</td>
<td>1.5±1.5</td>
<td>1.4±1.0</td>
</tr>
</tbody>
</table>
Figure 2. Flow-Mediated Dilatation and Nitroglycerin-Mediated Dilatation during the 6-Month Study Period.
CONCLUSIONS

Intensive periodontal treatment resulted in acute, short-term systemic inflammation and endothelial dysfunction. However, 6 months after therapy, the benefits in oral health were associated with improvement in endothelial function.
ED treatment

• Treatment should target the underlying comorbidity that lead to ED

• Life style modification – diet, exercise, smoking weight reduction

• NO pathways – L-arginine. PDE-I

• Receptor and enzyme pathways – beta blockers, ACE-I, angiotensin receptor blockers, statins, aspirin)
Secondary endothelial therapy

• Preserve the function of the already injured endothelium to delay progression of cardiovascular disease

• Statins, ACE-I, beta blockers, endothelin antagonists
### Table 1. Factors that cause and interventions that improve endothelial dysfunction

<table>
<thead>
<tr>
<th>Factors associated with endothelial dysfunction</th>
<th>Interventions that improve endothelial function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased age</td>
<td>L-arginine</td>
</tr>
<tr>
<td>Male sex</td>
<td>Antioxidants</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Smoking</td>
<td>Cholesterol lowering</td>
</tr>
<tr>
<td>Increased serum cholesterol</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Low serum HDL-cholesterol</td>
<td>Exercise</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Mediterranean Diet</td>
</tr>
<tr>
<td>Increased serum homocysteine</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>High-fat meal</td>
<td></td>
</tr>
</tbody>
</table>
• Endothelial barrier dysfunction in septic shock
  https://www.youtube.com/watch?v=yl6R_3Jrs_s
• NO and vasodilation
  https://www.youtube.com/watch?v=echVKswxTqQ
• Vascular endothelium
  http://www.authorstream.com/Presentation/nitinpuram-1516566-vascular-endothelium/
A short break
Venous insufficiency
Varices
Venous system of lower limbs

- Superficial
- Perforator
- Deep
Chronic venous disease

- 20% of Western population
- Varicose veins
- Chronic venous insufficiency
Varicose veins

• Dilated, often palpable, subcutaneous veins with reversed blood flow
• Mostly in legs
• 30% of population
• Risk factors: unknown, age, sex, pregnancy, obesity, family history
Pathogenesis

• **Reflux**
• Obstruction

• Varicose veins:
  • Increased amount of collagen
  • Decreased number of smooth muscle cells and elastin

• Disorganization of muscle components, disruption of elastin fibres and fibrosis

• **Weakness of vein wall** leads to dilatation and enlargement of the **valve ring** – the vein is unable to work properly - **reflux**
Pathogenesis

• **Descending** theory – the process starts proximally and expands distal

• **Ascending** theory – tributaries become dilated and incompetent and only thereafter the main trunks and junctions
Pathogenesis

• **Obstruction**

• **Acute** obstruction occurs in deep vein thrombosis

• **Chronic** obstruction caused by post-thrombotic changes – stenosis, occlusion, rigidity of vein wall

• Obstruction + reflux – in 55% of symptomatic patients
Figure 4. Contrasting Effects of Steady, Laminar Shear Stress (Panel A) and Turbulent or Reversing Shear Stress (Panel B) on Vessel Walls.
Evaluation

• **Clinical features**: limb pain, swelling, stasis, skin changes, ulceration

• **Symptoms**: itching, restless legs, nocturnal leg cramps, heaviness, discomfort

• Pain
Pain

• Assessed by **visual-analogue scale**, type and frequency of analgesic use
• Absent in 20% patients
• The only feature in 10% patients
• Is relieved by **leg elevation, support stockings, walking**
CEAP classification

- Clinical
- Etiologic
- Anatomical
- Pathophysiological

CVI = C₃-C₆
Figure 1. Clinical Manifestations of Chronic Venous Disease.
Telangiectases (clinical, etiologic, anatomical, and pathophysiological [CEAP] class C1) are shown in Panel A, varicose veins (CEAP class C2) in Panel B, pigmentation (CEAP class C3) in Panel C, and active ulceration (CEAP class C4) in Panel D.
### CEAP

<table>
<thead>
<tr>
<th>Clinical class</th>
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<tbody>
<tr>
<td>$C_0$</td>
<td>No venous disease</td>
</tr>
<tr>
<td>$C_1$</td>
<td>Spider Angioma</td>
</tr>
<tr>
<td>$C_2$</td>
<td>Varicose veins</td>
</tr>
<tr>
<td>$C_3$</td>
<td>Edema of venous etiology</td>
</tr>
<tr>
<td>$C_4$</td>
<td>Hyperpigmentation, Dermatitis, Lipodermatosclerosis.</td>
</tr>
<tr>
<td>$C_5$</td>
<td>Healed ulceration</td>
</tr>
<tr>
<td>$C_6$</td>
<td>Active ulceration</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiology</th>
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<tbody>
<tr>
<td>$E_C$</td>
<td>Congenital</td>
</tr>
<tr>
<td>$E_P$</td>
<td>Primary</td>
</tr>
<tr>
<td>$E_S$</td>
<td>Secondary</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Anatomy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_S$</td>
<td>Superficial Veins</td>
</tr>
<tr>
<td>$A_D$</td>
<td>Deep Veins</td>
</tr>
<tr>
<td>$A_P$</td>
<td>Perforating Veins</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathology</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_R$</td>
<td>Reflux</td>
</tr>
<tr>
<td>$P_O$</td>
<td>Obstruction</td>
</tr>
<tr>
<td>$P_{R,O}$</td>
<td>Reflux &amp; obstruction</td>
</tr>
</tbody>
</table>
Adjunctive scoring system

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1 (mild)</th>
<th>Score</th>
<th>3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>None</td>
<td>Occasional; no use of analgesics</td>
<td>Daily; occasional use of non-narcotic analgesics</td>
<td>Constant use of narcotic analgesics</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>None</td>
<td>Few, scattered</td>
<td>Multiple</td>
<td>Extensive</td>
</tr>
<tr>
<td>Edema</td>
<td>None</td>
<td>Evening, ankle only</td>
<td>Afternoon, above ankle</td>
<td>Morning above ankle</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>None</td>
<td>Limited</td>
<td>Diffuse over lower third of leg</td>
<td>Wide distribution</td>
</tr>
<tr>
<td>Inflammation and cellulitis</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Induration</td>
<td>None</td>
<td>Focal</td>
<td>Less than lower third of leg</td>
<td>Entire lower third of leg or more</td>
</tr>
<tr>
<td>Active ulcers — no.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Duration of active ulceration — mo</td>
<td>None</td>
<td>&lt;3</td>
<td>3–12</td>
<td>Not healed at &gt;12</td>
</tr>
<tr>
<td>Diameter of active ulcer — cm</td>
<td>None</td>
<td>&lt;2</td>
<td>2–6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Use of stockings</td>
<td>None</td>
<td>Occasional</td>
<td>Most days</td>
<td>Constant</td>
</tr>
</tbody>
</table>

*An aggregate score for the limb is calculated by adding the individual component scores. The range of the total score is 0 to 30.*
Imaging

• Duplex ultrasound scan
Complications

• Deep vein thrombosis
• Skin changes
• Leg ulcers (3% patients)
• Bleeding
• Thrombophlebitis – thrombus in superficial vein
Treatment

Varicose veins: diagnosis and management

Clinical guideline
Published: 24 July 2013
nice.org.uk/guidance/cg168

Editor’s Choice — Management of Chronic Venous Disease
Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)

ESVS Guidelines Committee b P. Kolh, G.J. de Borst, N. Chakfé, S. Debus, R. Hinchliffe, I. Koncar, J. Lindholt, M.V. de Ceniga, F. Vermassen, F. Verzini,
Treatment

• Goals:
  • Alleviate symptoms
  • Prevent severe complications (ulcers)

• 1. Endothermal ablation of the saphenous vein – burn the vein from inside (radiofrequency or laser)
• 2. Foam sclerotherapy
• 3. Surgery
• 4. Compression hosiery (only if no other intervention is suitable)
Advice

• Weight loss
• Light to moderate physical activity
• Avoid factors that make symptoms worse
• When and where to seek further medical help
BOX 1. WHEN TO REFER TO A VASCULAR SERVICE

Patients should be referred to the vascular service if any of the following are observed:

- Bleeding from the varicose veins - in this situation, the referral must be made immediately
- Symptomatic primary or symptomatic recurrent varicose veins
- Lower-limb skin changes, such as pigmentation or eczema, thought to be caused by chronic venous insufficiency
- Superficial vein thrombosis (characterised by the appearance of hard, painful veins) and suspected venous incompetence
- A venous leg ulcer (a break in the skin below the knee that has not healed within two weeks)
- A healed venous leg ulcer
Treatment in pregnancy

• Pregnancy can exacerbate symptoms of varicose veins and cause new ones
• **No intervention** in pregnancy (increases risk of thrombosis)
• Compression hosiery should be used