Microvascular dysfunction
In obesity or metabolic syndrome

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Microcirculation (Definition & Functions)

- Microcirculation: vessels <150 m in diameter.
  - Includes arterioles, capillaries, and venules.
- Current definition
  - based on arterial vessel physiology rather than diameter
  - depending on the response of the isolated vessel to increased internal pressure.
Microcirculation (Definition & Functions)

• By new definition
  - all vessels that respond to increasing pressure by a myogenic reduction in lumen diameter
    → considered part of the microcirculation.
• Such a definition would include the smallest arteries and arterioles in the microcirculation in addition to capillaries and venules.
Functions of the microcirculation

- Optimize the delivery of nutrients and removal of waste products from all cells of the body in response to variations in demand.
- Avoid large fluctuations in hydrostatic pressure at the level of the capillaries that otherwise would impair capillary exchange.
Microcirculation (Definition & Functions)

- In pathological conditions (e.g., obesity)
  - loss of autoregulatory mechanisms
  - development of microvascular dysfunction.

![Diagram showing the relationship between obesity-related endocrine signaling, insulin resistance, impaired capillary recruitment, and type-2 diabetes](image-url)
Microvascular Dysfunction in Obesity
Evidence from several studies indicates that obesity impairs microvascular function in several ways.

1. **Impairments of endothelial function** of different microvascular structures

   - Obese subjects showed blunted vasodilation in response to classic endothelium-dependent vasodilators in skin and resistance arteries.
Effect of exercise training on FBF. A, FBF response to ACh in overweight nondiabetics (n = 7, left) and type 2 diabetics (n = 13, right) (o, pretraining values; *, posttraining values); B, arterial occlusion (reactive hyperemia) after 8-wk exercise in overweight nondiabetics (n = 5, left) and in type 2 diabetics (n = 10, right); C, FBF response to SNP in overweight nondiabetics (n = 7, left) and type 2 diabetics (n = 13, right) (o, pretraining values; *, posttraining values). Blood flow in the contralateral arm not infused with ACh or SNP is shown by dashed lines. Data are means ± SE. *, P < 0.05 vs. pretraining.
Microvascular Dysfunction in Obesity

Endothelial dysfunction

- Diminished vasodilator function of resistance vessels and capillary recruitment to reactive hyperemia and shear stress
  - Observation in the microcirculation of the skin, using nailfold capillaroscopy.
Microvascular measurements before start of infusions and after 2-hour infusions of insulin or saline

Decreased sensitivity of resistance vessels to insulin-induced endothelium-dependent vasodilation.
Femoral arteriovenous glucose difference (A), leg blood flow (B), and leg glucose uptake (C) as a function of prevailing serum insulin concentration.

Figure 2. Femoral arteriovenous glucose difference (A), leg blood flow (B), and leg glucose uptake (C) as a function of prevailing serum insulin concentration during euglycemic clamp studies in lean (●) and obese (○) subjects. Solid lines depict the fit based on a four-parameter logistic equation.
2. Structural impairments of the microvasculature

The skeletal muscle circulation of obese Zucker rats shows decreased capillary density, so-called rarefaction, and structural remodeling.

![Graph showing microvascular density across different experiment groups.](image)

**Fig. 4.** Data (mean ± SEM) describing gastrocnemius muscle microvessel density (A) in LZR and OZR at 16–17 wk of age under the conditions of the present study. *P < 0.05 vs. untreated LZR; †P < 0.05 vs. untreated OZR; ‡P < 0.05 vs. OZR treated with tempol.

Frisbee JC. Am J Physiol Regul Integr Comp Physiol 2005;289:R307-R316
Recent studies of obese individuals have also demonstrated this capillary rarefaction in human skeletal muscle.

Photomicrographs of muscle stained for capillaries in young lean (A) and obese (B) men. Capillaries appear as dark-stained regions between fibers. Type I fibers stain as dark and type II fibers stain as light. Bar = 50 µm.

Stimulation of AT1 or AT2 receptor regulates vascular remodeling and atherosclerosis in concert with insulin receptor signaling in insulin-resistant state

Microvascular Dysfunction in Obesity

- Weight loss improve endothelial function.

**TABLE 5. Relationships of Reduction of Anthropometric Measures After Weight Loss In Obese Women With Reduction of Proinflammatory Cytokines and Adhesion Molecules and Improvement of Endothelial Functions**

<table>
<thead>
<tr>
<th>Measure</th>
<th>BMI</th>
<th>WHR</th>
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<tbody>
<tr>
<td>TNF-α*</td>
<td>0.35‡</td>
<td>0.54§</td>
</tr>
<tr>
<td>IL-6*</td>
<td>0.31‡</td>
<td>0.45§</td>
</tr>
<tr>
<td>P-selectin</td>
<td>0.29‡</td>
<td>0.34‡</td>
</tr>
<tr>
<td>VCAM-1</td>
<td>0.25†</td>
<td>0.29‡</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>0.22†</td>
<td>0.25†</td>
</tr>
<tr>
<td>MBP response to L-arginine</td>
<td>–0.24†</td>
<td>–0.29‡</td>
</tr>
<tr>
<td>PA response to L-arginine</td>
<td>–0.21†</td>
<td>–0.24†</td>
</tr>
</tbody>
</table>

*Log-transformed; †P<0.05; ‡P<0.02; §P<0.01. MBP indicates mean blood pressure; and PA, platelet aggregation.

Conclusion

- Clear association between obesity and microvascular dysfunction, possibly via the endothelium, in different tissues has been established.
Microvascular Dysfunction And Insulin Resistance
Microvascular Dysfunction and Insulin Resistance

- Insulin resistance
  - decreased sensitivity for insulin-mediated glucose disposal.

- A major action of insulin in muscle and adipose tissue involves translocation of the insulin-responsive glucose transporter (GLUT4) to the cell surface
  → leading to glucose uptake in peripheral tissues.
Microvascular Dysfunction and Insulin Resistance

- This requires phosphatidylinositol (PI3)-kinase-dependent signaling pathways.

• In addition to this metabolic action, insulin has **two discrete actions** on the arterial vasculature to promote the delivery of insulin and glucose to skeletal muscles.
In the 1990s, Baron and colleagues were the first to report insulin’s ability to vasodilate and consequently increase total skeletal muscle blood flow.

- Bulk blood flow was paralleled by an increase in insulin-mediated glucose uptake.

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole body glucose uptake</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum (μmol/M² per min)</td>
<td>460</td>
<td>468</td>
</tr>
<tr>
<td>Maximum (μmol/M² per min)</td>
<td>2,719</td>
<td>2,334*</td>
</tr>
<tr>
<td>ED₅₀ for insulin (pmol/liter)</td>
<td>515</td>
<td>1,263*</td>
</tr>
<tr>
<td><strong>Arteriovenous blood glucose difference</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum (mmol/liter)</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Maximum (mmol/liter)</td>
<td>1.84</td>
<td>1.38*</td>
</tr>
<tr>
<td>ED₅₀ for insulin (pmol/liter)</td>
<td>391</td>
<td>987*</td>
</tr>
<tr>
<td><strong>Leg blood flow</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum (dl/min)</td>
<td>2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Maximum (dl/min)</td>
<td>4.3</td>
<td>4.4</td>
</tr>
<tr>
<td>ED₅₀ for insulin (pmol/liter)</td>
<td>266</td>
<td>957*</td>
</tr>
<tr>
<td><strong>Leg glucose uptake</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum (μmol/leg per min)</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Maximum (μmol/leg per min)</td>
<td>811</td>
<td>605*</td>
</tr>
<tr>
<td>ED₅₀ for insulin (pmol/liter)</td>
<td>420</td>
<td>1,153*</td>
</tr>
</tbody>
</table>

Minimum and maximum values represent rates of whole body glucose uptake, arteriovenous glucose difference, leg blood flow, and rates of leg glucose uptake at 0 and infinite insulin concentrations, respectively.

* P < 0.01, obese vs. lean.

As a consequence, the physiological importance, in stimulating glucose uptake, of insulin’s ability to increase total blood flow is doubtful.
Insulin induces a second vascular action further down the arterial tree, termed functional capillary recruitment.
• By reducing precapillary arteriolar tone, insulin redirects blood flow within the microvascular bed from non-nutritive to nutritive vessels

→ resultant increase in the overall number of perfused capillaries.
- Insulin-induced capillary recruitment has been shown to require physiological concentrations of insulin with a time course that approximates the time course for insulin-mediated glucose uptake in skeletal muscle.

In human muscle, insulin increased microvascular blood volume.

Coggins M et al. Diabetes 2001;50: 2682–2690
Both human and rat studies underline this coupling.

Obese Zucker rats are characterized by both impaired insulin-induced glucose uptake and impaired capillary recruitment in the basal state and during hyperinsulinemia.

In human obesity, similar impairments have recently been demonstrated.

These findings suggest the involvement of microvascular dysfunction in the development of obesity-related insulin resistance.

In terms of cause and effect, there is support for the suggestion that microvascular dysfunction precedes and even predicts the development of insulin resistance and Type 2 diabetes.

Meigs JB et al. Diabetes 2006;55: 530–537
Wong TY et al. JAMA 2002;287: 2528–2533
This idea is also supported by studies showing endothelial dysfunction in mildly overweight, normoglycemic subjects with a strong family history of Type 2 diabetes mellitus.

Thank You
참고자료
Coronary microvascular remodelling and dysfunction is common in human diseases

HCM  Diabetes  Hypertension
Mechanisms of Diabetic Microvascular Disease

### Table 2: Examples of Mechanisms Implicated in Diabetic Microvascular Disease Secondary to Hyperglycemia

<table>
<thead>
<tr>
<th>Increased Aldose Reductase Pathway</th>
<th>Protein Kinase Activation</th>
<th>Increased Oxidative Stress</th>
<th>Protein Glycation</th>
<th>Increased Hexosamine Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Sorbitol</td>
<td>↑ VEGF</td>
<td>↑ ROS</td>
<td>↑ AGE</td>
<td>↑ PAI-1</td>
</tr>
<tr>
<td>Osmotic cellular damage</td>
<td>↑ ROS</td>
<td></td>
<td>Apoptotic death</td>
<td>Inhibition of eNOS activity</td>
</tr>
<tr>
<td>↓ (Na⁺ and K⁺) ATPase activity</td>
<td>NF-κB activation</td>
<td></td>
<td>NF-κB activation</td>
<td></td>
</tr>
<tr>
<td>↑ NADH/NAD⁺</td>
<td>Inhibition of eNOS activity</td>
<td></td>
<td>↑ ROS</td>
<td></td>
</tr>
<tr>
<td>↓ NADPH</td>
<td>↑ Endothelin-1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ATPase = adenosine triphosphatase; eNOS = endothelial nitric oxide synthase; NAD = nicotinamide adenine dinucleotide; NADH = nicotinamide adenine dinucleotide reduced; NADPH = nicotinamide adenine dinucleotide phosphate reduced; PAI = plasminogen activator inhibitor; ROS = reactive oxygen species; VEGF = vascular endothelial growth factor; other abbreviations as in Table 1.

AGE = advanced glycation end products; IL = interleukin; MCP = monocyte chemoattractant protein; NF-κB = nuclear factor-kappa B; NO = nitric oxide.
Figure 4. Shared features of glucotoxicity, lipotoxicity, and inflammation are shown, illustrating the key pathways and potential linkage between these conditions. Glucotoxicity leads to insulin resistance, which in turn contributes to diabetes, obesity, and dyslipidemia. Lipotoxicity, driven by oxidative stress, pro-inflammatory signaling, and ceramide, also contributes to insulin resistance and endothelial dysfunction. Inflammation is mediated by pro-inflammatory factors and kinases/transcription factors, which can exacerbate the processes of glucotoxicity and lipotoxicity. This diagram highlights the complex interplay and potential therapeutic targets for diseases such as CAD, hypertension, and atherosclerosis.