Inflammation, Obesity, and Diabetes

20.380 S'10
How big of a problem is Diabetes worldwide?

Projected totals, in millions

Courtesy of International Diabetes Federation. Used with permission.
Obesity Trends* Among U.S. Adults
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)
Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

**Obesity (BMI ≥30 kg/m²)**

- **1994**
- **2000**
- **2008**

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;14.0%</th>
<th>14.0-17.9%</th>
<th>18.0-21.9%</th>
<th>22.0-25.9%</th>
<th>≥26.0%</th>
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<tbody>
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<td>1994</td>
<td></td>
<td></td>
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<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;14.0%</td>
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<tr>
<td>2008</td>
<td></td>
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<td></td>
<td></td>
<td>14.0-17.9%</td>
</tr>
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</table>

No Data are noted when data are not available.


**Diabetes**

- **1994**
- **2000**
- **2008**

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;4.5%</th>
<th>4.5-5.9%</th>
<th>6.0-7.4%</th>
<th>7.5-8.9%</th>
<th>≥9.0%</th>
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<tr>
<td>1994</td>
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<tr>
<td>2000</td>
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<td>&lt;4.5%</td>
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<tr>
<td>2008</td>
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<td></td>
<td></td>
<td></td>
<td>4.5-5.9%</td>
</tr>
</tbody>
</table>

No Data are noted when data are not available.
Normal Physiology and Insulin Effects

Insulin Action

- Pancreas
- Liver
- Adipocytes

- Glycogen storage
- Gluconeogenesis
- Glucose Uptake

Glucose

Fruits and vegetables photo courtesy of val’sphotos on Flickr. Pancreas and liver images from US HHS. Muscle and adipocyte images by MIT OpenCourseWare.
Insulin Resistance – Positive Feedback

**Insulin Resistance**

- Glucose
- Pancreas
- Liver
  - Gluconeogenesis
  - Increased Glucose
- Muscle
  - Glucose Uptake
  - Increased Glucose
- Adipocytes
  - Glucose Uptake
  - Increased Glucose

Burger and fries photo courtesy of stu_spivack on Flickr. Pancreas and liver images from US HHS. Muscle and adipocyte images by MIT OpenCourseWare.
FIGURE 1. Natural course of type 2 diabetes, a generalized and simplified scheme. Programming of metabolic regulation and gene expression occurs in utero. Insulin resistance with or without obesity develops in childhood, adolescence, or early adulthood and is compensated by increased beta cell mass and insulin secretion. Probably in response to obesity/fat cell stress macrophages invade fat tissue and give rise to local inflammation ("adipositis"). The failure of islets to compensate for increased insulin demand is primarily caused by beta cell death. This leads to IGT and eventually to overt T2DM. Evidence of systemic low grade inflammation and of oxidative stress/mitochondrial dysfunction is noted from early on.
Phenotyping Insulin Resistance

Kim et al., J. Clinical Investigation 2007, 117, 2621-2637

Phenotyping Insulin Resistance

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>ob/ob</th>
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</thead>
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<tr>
<td>Glucose (mg/dl)</td>
<td>92.4 ± 11.6A</td>
<td>313.8 ± 76.6</td>
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<tr>
<td>Insulin (ng/ml)</td>
<td>1.83 ± 0.51B</td>
<td>7.85 ± 1.02</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>147.2 ± 27.34B</td>
<td>300.37 ± 114.2</td>
</tr>
<tr>
<td>FFA (mmol/l)</td>
<td>2.05 ± 0.93</td>
<td>3.13 ± 0.13</td>
</tr>
</tbody>
</table>

Glucose Tolerance Test

Furuhashi et al., Nature 2007, 447, 959-965

Insulin Tolerance Test

Insulin Signaling Network Overview


Complex signaling on Insulin receptor substrates


IRS proteins play key roles in regulating insulin function.

Adipocytes – key regulators of insulin action

Adipocyte Functions

- Glucose Uptake
- Adipocytokine Release
- Free Fatty Acid Release
- Triglyceride Storage
- Adipose Hormone Release

Slide courtesy of Bryan Owens and Emily Miraldi. Used with permission.
Adipocytes in insulin resistance

Adipocyte Functions

- Adipocytokine Release
- Glucose Uptake
- Triglyceride Storage
- Free Fatty Acid Release
- Adipose Hormone Release

Modified

Slide courtesy of Bryan Owens and Emily Miraldi. Used with permission.
The beginning (?) – ER stress, the unfolded protein response, and inflammation

NFκB target genes:

- IL-1β
- TNF-α
- IL-6
- IL-6
- MCP-1 (monocyte chemotactant protein 1) (CCL2)
- Interferon β
- +many, many others including pro- and anti-inflammatory genes

Overnutrition leads to increased adipocyte size and macrophage recruitment

LEAN
Nutrient excess
Expansion of fat mass
Adipocyte production of cytokines and chemokines
Endothelial cell expression of adhesion molecules
Monocyte recruitment and differentiation
Macrophage infiltration and cytokine production

OBSESE
Insulin resistance
Proinflammatory and proatherogenic mediators
Atherosclerosis


Shoelson, Gastroenterology (2007) 132, 2169-2180
More granularity – increased adiposity and inflammation

How does macrophage recruitment affect insulin resistance in adipocytes?

Complex signaling on Insulin receptor substrates

Free fatty acids, TNF, and NO drive insulin resistance

IL-6, TNF-α, etc


De Luca and Olefsky, FEBS letters, 2008
Where do free fatty acids come from?

Multiple sources, including diet and adipocytes

\[ \beta \text{-oxidation in muscle mitochondria (exercise)} \]

---

More granularity of FFA release from adipocytes


Saturated free fatty acids lead to JNK activation and to IRS phosphorylation on Thr-307
Free fatty acids also bind to TLR’s and FABPs, driving insulin resistance through multiple mechanisms.

NF-κB
STAT activation
IRS phosphorylation

IL-10
Adiponectin

If TLR’s play a critical role in this process, why not target them in insulin resistance?

Shi et al, JCI, 2006, 116

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TLR4⁻/⁻ looks promising for IR?

Increased weight gain, but....

Overall improved insulin sensitivity in fat, even with weight gain
Free fatty acids also bind to TLR’s and FABPs, driving insulin resistance through multiple mechanisms.

IL-10
Adiponectin

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology.

Hotamisligil and Erbay, Nat. Reviews Immunology, 2008
Another interesting target: FABPs

Multiple other knock-out mice with IR phenotypes

Table 1. Knockout Mice With Potentially Relevant Metabolic Phenotypes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>Mature onset obesity and insulin resistance(^{65})</td>
</tr>
<tr>
<td>TNF-(\alpha)</td>
<td>Improved insulin sensitivity and insulin signalling(^{78})</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Improved insulin sensitivity(^{103})</td>
</tr>
<tr>
<td>IL-18</td>
<td>Hyperphagia, obesity, and insulin resistance(^{125})</td>
</tr>
<tr>
<td>IL-1(\alpha)</td>
<td>Lower fasting glucose and insulin with improved insulin sensitivity(^{81})</td>
</tr>
<tr>
<td>Resistin</td>
<td>Improved glucose tolerance on HFD(^{126})</td>
</tr>
<tr>
<td>MCP-1</td>
<td>Decreased monocyte recruitment to adipose tissue, decreased adiposity, hepatic steatosis, and insulin resistance(^{10,39})</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>Exacerbation of obesity and increased susceptibility to diet-induced insulin resistance(^{127})</td>
</tr>
<tr>
<td>iNOS</td>
<td>Protection against HFD-induced insulin resistance(^{128})</td>
</tr>
<tr>
<td>IKK(\beta)</td>
<td>Improved insulin sensitivity(^{17,49})</td>
</tr>
<tr>
<td>JNK1</td>
<td>Improvement of insulin resistance in diet-induced and genetic obesity(^{52})</td>
</tr>
<tr>
<td>SOCS1</td>
<td>Decreased blood glucose levels and sustained insulin receptor phosphorylation(^{129})</td>
</tr>
</tbody>
</table>

ICAM, intracellular adhesion molecule; iNOS, inducible nitric oxide synthase; SOCS, suppressors of cytokine signaling.

Adipocytokines in lean and obese states

Figures removed due to copyright restrictions.
See Figures 1 and 2 from Tilg and Moschen,
Adiponectin – anti-inflammatory adipocytokine

Figures removed due to copyright restrictions.
See Figures 1 and 2 from Tilg and Moschen,
Adiponectin – anti-inflammatory adipocytokine

Adiponectin as a primary systemic therapy?

The adiponectin $^{ob/ob}$ mouse

Taubes 17 JULY 2009  VOL 325  SCIENCE  www.sciencemag.org
Adiponectin overexpression effects

Images removed due to copyright restrictions. See Figure 1, A and B, and Table 1 from Kim, J-Y., et al. "Obesity-Associated Improvements in Metabolic Profile Through Expansion of Adipose Tissue." J Clinical Investigation 117 (2007): 2621-2637. http://dx.doi.org/10.1172/JCI31021.
Adverse(?) adiponectin overexpression effects

Image removed due to copyright restrictions. See Figure 3 from Kim, J-Y., et al. "Obesity-Associated Improvements in Metabolic Profile Through Expansion of Adipose Tissue." J Clinical Investigation 117 (2007): 2621-2637. http://dx.doi.org/10.1172/JCI31021.
Positive adiponectin overexpression effects

Image removed due to copyright restrictions. See Figure 3 (G & I) and 4 (E) from Kim, J-Y., et al., "Obesity-Associated Improvements in Metabolic Profile Through Expansion of Adipose Tissue." J Clinical Investigation 117 (2007): 2621-2637.
Adipocytokines in lean and obese states

Insulin activation leads to leptin release – a slow negative feedback loop to shut down the Insulin signal

Leptin – pro-inflammatory adipocytokine

If inflammation is bad and adiponectin is good, then leptin must be bad?

The ob/ob mouse and the db/db mouse:

Mouse models of obesity and diabetes in which leptin or leptin receptor is knocked out or dysfunctional.

Why are these mice obese and diabetic? Appetite – leptin signaling in the hypothalamus leads to transcriptional regulation of neuropeptides which can either promote feeding and weight gain (‘orexigenic’ peptides) or those that suppress feeding and weight (‘anorexigenic’ peptides).

Leptin suppresses neuropeptide Y (NPY) and agouti-related peptide (AgRP), while increasing α-melanocyte stimulating hormone (MSH) and cocaine- and amphetamine regulated transcript (CART).
Leptin plays a very complex systemic role

Overfeeding, acute-phase response, inflammation (IL-1 and TNF) and insulin

Central effects
- Stomach, skeletal muscle and placenta
- Leptin
- Adipose tissue
- Fasting, reduced food intake and testosterone

Peripheral effects
- T-cell function
- Haematopoiesis
- Angiogenesis
- Pancreatic β-cell function
- Reproductive function
- Basal metabolism

Central nervous system and hypothalamus
- Food intake
- HPA hormones
- Bone formation and remodelling

CRH
ACTH
HPA axis

IL-1, IL-6
TNF and leptin

Pericellular

Glucocorticoids

Thymus

Lymph node

T cells

Simple leptin signaling

Leptin resistance:
- SOCS3
- STAT activation
- PTP1b

Druggable target?


La Cava and Matarrese, Nat. Rev. Immunol. 2004
Leptin affects immune response, loss of leptin reduces autoimmune diseases

<table>
<thead>
<tr>
<th>Disease model</th>
<th>Susceptibility of ob/ob mice</th>
<th>Cytokines and inflammatory factors involved</th>
<th>Antibodies present</th>
<th>Effects of leptin administration</th>
<th>Refs</th>
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</thead>
<tbody>
<tr>
<td>EAE</td>
<td>Reduced/resistant</td>
<td>Increased IL-4; absent IFN-γ after myelin-specific stimulation of T cells</td>
<td>Increased myelin-specific IgG1; reduced IgG2a</td>
<td>Restores IFN-γ secretion and disease susceptibility is comparable to wild-type mice; promotes myelin-specific antibody switch from IgG1 to IgG2a</td>
<td>52,53</td>
</tr>
<tr>
<td>AIA</td>
<td>Reduced/resistant</td>
<td>Increased IL-10; reduced IFN-γ after mBSA stimulation of T cells; reduced synovial IL-1β and TNF</td>
<td>Decreased serum antibody specific for mBSA</td>
<td>N.D.</td>
<td>51</td>
</tr>
<tr>
<td>EIC</td>
<td>Reduced/resistant</td>
<td>Reduced IFN-γ, TNF, IL-1β, IL-6, IL-10 and IL-18; reduced chemokines CCL3 and CXCL2; reduced MPO activity; reduced COX2 expression</td>
<td>N.D.</td>
<td>Restores normal secretion of IFN-γ, TNF, IL-1β, IL-6, IL-10 and IL-18; restores disease susceptibility to a level comparable to wild-type mice</td>
<td>56</td>
</tr>
<tr>
<td>EIH</td>
<td>Reduced/resistant</td>
<td>Reduced serum TNF and IL-18</td>
<td>N.D.</td>
<td>Restores TNF and IL-18 secretion; restores disease susceptibility to a level comparable to wild-type mice</td>
<td>37,50</td>
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<tr>
<td>EINN</td>
<td>Reduced/resistant</td>
<td>Undetectable in vitro proliferative and cytokine T-cell responses against sheep IgG; reduced glomerular IgG deposition</td>
<td>Reduced or no difference in sheep-IgG-specific serum antibodies</td>
<td>N.D.</td>
<td>59</td>
</tr>
</tbody>
</table>


La Cava and Matarese, Nat. Rev. Immunol. 2004
Resistin, another pro-inflammatory adipocytokine (?)

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology.

Tilg and Moschen, Nat. Rev. Immunol. 2006, 6, 772-783
# Effects of adipocytokines – a reference table

<table>
<thead>
<tr>
<th>Adipocytokine</th>
<th>Inflammatory effect</th>
<th>Effects on immunity</th>
<th>Adaptive</th>
<th>Associated diseases</th>
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<tr>
<td>Adiponectin</td>
<td>Anti-inflammatory</td>
<td>↓ Endothelial adhesion molecules&lt;sup&gt;40&lt;/sup&gt;</td>
<td>↓ B-cell lymphopoiesis&lt;sup&gt;117&lt;/sup&gt;</td>
<td>Insulin resistance and type 2 diabetes mellitus&lt;sup&gt;33,35&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>↓ NF-κB&lt;sup&gt;40,41,43&lt;/sup&gt;</td>
<td>↓ T-cell responses&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Atherosclerosis&lt;sup&gt;57,58,60&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>↓ TNF&lt;sup&gt;35&lt;/sup&gt;</td>
<td></td>
<td>Experimentally induced liver disease: non-alcoholic and alcoholic fatty liver disease&lt;sup&gt;49&lt;/sup&gt;, CCl&lt;sub&gt;4&lt;/sub&gt; liver fibrosis (REF. 50); LPS-treated KK-AY mice (REF. 51); and experimentally induced hepatitis (ConA)&lt;sup&gt;12&lt;/sup&gt;</td>
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<td></td>
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<td>↓ IL-6 (REF. 42)</td>
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<td>Cardiac injury&lt;sup&gt;55,56&lt;/sup&gt;</td>
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<td></td>
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<td>↑ IFNγ&lt;sup&gt;42&lt;/sup&gt;</td>
<td></td>
<td>Cancer&lt;sup&gt;102,103&lt;/sup&gt;</td>
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<td>↑ IL-10 (REF. 42)</td>
<td></td>
<td>Inflammatory bowel disease&lt;sup&gt;112&lt;/sup&gt;</td>
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<td>↑ IL-1RA&lt;sup&gt;42&lt;/sup&gt;</td>
<td></td>
<td>Rheumatoid arthritis&lt;sup&gt;115&lt;/sup&gt;</td>
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<td>↓ Phagocytosis&lt;sup&gt;42&lt;/sup&gt;</td>
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<td></td>
<td>Pro-inflammatory</td>
<td>↑ CXCL8 in presence of LPS&lt;sup&gt;44&lt;/sup&gt;</td>
<td>ND</td>
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<td>Leptin</td>
<td>Pro-inflammatory</td>
<td>↑ TNF&lt;sup&gt;58,71&lt;/sup&gt;</td>
<td>↑ Lymphopoiesis&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Insulin resistance&lt;sup&gt;9&lt;/sup&gt;</td>
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<td>↑ IL-6 (REF. 68)</td>
<td>↑ Thymocyte survival&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Experimentally induced hepatitis (ConA)&lt;sup&gt;59,76&lt;/sup&gt;</td>
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<td>↑ IL-12 (REF. 68)</td>
<td>↑ T-cell proliferation&lt;sup&gt;64&lt;/sup&gt;</td>
<td>EAE and antigen-induced arthritis&lt;sup&gt;67,77&lt;/sup&gt;</td>
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<td>↑ Neutrophil activation (CD11b)&lt;sup&gt;70&lt;/sup&gt;</td>
<td>↑ T&lt;sub&gt;h&lt;/sub&gt;1 response (IL-2 and IFNγ)&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Experimentally induced colitis: CD4&lt;sup&gt;+&lt;/sup&gt;CD45RB&lt;sup&gt;+&lt;/sup&gt; T-cell transfer&lt;sup&gt;78&lt;/sup&gt;; and IL-10-deficient mice&lt;sup&gt;133&lt;/sup&gt;</td>
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<td>↑ ROS&lt;sup&gt;70&lt;/sup&gt;</td>
<td>↓ T&lt;sub&gt;h&lt;/sub&gt;2 response (IL-4)&lt;sup&gt;64&lt;/sup&gt;</td>
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<td>↑ Chemotaxis&lt;sup&gt;70&lt;/sup&gt;</td>
<td></td>
<td>Asthma&lt;sup&gt;110&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>↑ NK-cell function&lt;sup&gt;72&lt;/sup&gt;</td>
<td></td>
<td>Cancer&lt;sup&gt;104&lt;/sup&gt;</td>
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<tr>
<td>Resistin</td>
<td>Pro-inflammatory</td>
<td>↑ TNF&lt;sup&gt;58,57&lt;/sup&gt;</td>
<td>ND</td>
<td>Insulin resistance (mice)&lt;sup&gt;5&lt;/sup&gt;</td>
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<td>↑ IL-1β&lt;sup&gt;86&lt;/sup&gt;</td>
<td>Type 2 diabetes mellitus (mice)&lt;sup&gt;80&lt;/sup&gt;</td>
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<td>↑ IL-6 (REF. 86)</td>
<td>Rheumatoid arthritis&lt;sup&gt;86&lt;/sup&gt;</td>
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<td>↑ IL-12 (REF. 86)</td>
<td>Atherosclerosis&lt;sup&gt;92&lt;/sup&gt;</td>
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<td>↑ NF-κB&lt;sup&gt;89&lt;/sup&gt;</td>
<td>Non-alcoholic fatty liver disease&lt;sup&gt;118&lt;/sup&gt;</td>
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<td></td>
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<td>↑ Endothelial adhesion molecules (VCAM1 and ICAM1)&lt;sup&gt;88&lt;/sup&gt;</td>
<td>Chronic kidney disease&lt;sup&gt;94&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Visfatin</td>
<td>ND</td>
<td>↑ IL-6 (REF. 119)</td>
<td>ND</td>
<td>Insulin resistance and type 2 diabetes mellitus&lt;sup&gt;95&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ IL-8 (REF. 119)</td>
<td>Acute lung injury&lt;sup&gt;97&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Apoptosis of neutrophils&lt;sup&gt;98&lt;/sup&gt;</td>
<td>Sepsis&lt;sup&gt;98&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

CCI<sub>4</sub>, carbon tetrachloride; ConA, concanavalin A; CXCL, CXC-chemokine ligand; EAE, experimental autoimmune encephalomyelitis; ICAM, intercellular adhesion molecule; IFNγ, interferon-γ; IL, interleukin; IL-1RA, IL-1 receptor antagonist; LPS, lipopolysaccharide; ND, not determined; NF-κB, nuclear factor-κB; NK, natural killer; ROS, reactive oxygen species; T<sub>h</sub>, T helper; TNF, tumour-necrosis factor; VCAM, vascular cell-adhesion molecule.

Two views of the key drivers of insulin resistance

http://dx.doi.org/10.1126/science.325_256
What about the adaptive Immune Response?

Current Treatment Options

GLP1 = glucagon like peptide 1
DPP4 = dipeptidyl peptidase 4

Source: Ashiya, M., and R. E. T. Smith. "Non-Insulin Therapies for Type 2 Diabetes."

Ashiya and Smith, Nat. Rev. Drug Disc. 2007
Thiazolidinediones (TZD’s) for insulin resistance/diabetes

Troglitazone, Rosiglitazone, Pioglitazone

Mechanism:
- PPAR-g agonists activate/repress transcription of PPARg target genes
- Adiponectin increases, along with beneficial effects (anti-inflammatory)
- Leptin decreases (increased appetite)
- Increased triglyceride storage
- Decreased synthesis of TNF-a, other pro-inflammatory signals (including MCP-1)

Benefits:
- Increased insulin sensitivity – decreased basal glucose and insulin levels

Downside
- Weight gain – increased adiposity, increased TG storage with increased adiponectin
- Coming off of TZD’s typically not an option
- Not a cure – more effective to stabilize disease
Metformin and AICAR for insulin resistance/diabetes

Metformin and AICAR activate AMPK, potentially through LKB1

Salicylates as a novel therapeutic option

Targets: Cyclooxygenase 1,2; IKKB - NFkB

Image removed due to copyright restrictions. See Figure 1 in Yuan, M., et al. "Reversal of Obesity- and Diet-Induced Insulin Resistance with Salicylates or Targeted Disruption of Ikkβ." *Science* 293, no. 5535 (August 31, 2001): 1673-1677.
Salicylates as a novel therapeutic option

Resveratrol and Sirtuins as modulators of insulin signaling?

Sun et al, Cell Metabolism, 2007

Hotamisligil and Erbay, Nat. Reviews Immunology, 2008

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology.

The multiple positive effects of red wine
Resveratrol, a SIRT1 agonist

E

C

Glucose uptake (% of control)

Insulin

Res (µM)

- 0.01 0.1 1 0.01 0.1 1

- + - + - + - +

Normal conditions

Insulin
Res (µM)

- 0.01 0.1 1 0.01 0.1 1

- + - + - + - +

p-Tyr1146-InsR
InsR
p-Ser473-Akt
p-Thr308-Akt
Akt
p-Ser9-Gsk3β
p-Ser241-PDK1
Sirt1
Tubulin


Sun et al, Cell Metabolism, 2007
The multiple positive effects of red wine
Resveratrol, a SIRT1 agonist


Sun et al, Cell Metabolism, 2007
Targeting mTORC1 as an insulin sensitizer?

Rapamycin hits mTORC2 (Akt activation complex)

mTORC1 is one of the key nutrient sensors

Diet and exercise as the most effective therapeutic?

Exercise Effects

- Increased mitochondrial activity, increased B-oxidation of fatty acids
- Decreased ATP, increased AMP
- Increased AMPK activity
- Decreased blood glucose
- Decreased basal insulin levels
- Increased leptin and insulin sensitivity

Diet Effects

- Decreased food intake → decreased mTOR activation, decreased ER stress
- Less saturated fat → decreased JNK activation
- Smaller, leaner adipocytes → less macrophage recruitment, less inflammation
- Improved insulin and leptin response → decreased appetite

One very powerful strategy – targeting appetite through leptin or GLP-1 (or other gut hormones)
At the end, it all comes back to caloric intake.

**Insulin Resistance**

At the end, it all comes back to caloric intake.

**Insulin**

Glucose → Pancreas → Insulin → Liver → Gluconeogenesis → Increased Glucose

Muscle → Glucose Uptake → Increased Glucose

Adipocytes → Glucose Uptake → Increased Glucose

**Burger and fries photo courtesy of stu_spivack on Flickr. Pancreas and liver images from US HHS. Muscle and adipocyte images by MIT OpenCourseWare.**