Pathophysiology of type 2 diabetes mellitus

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Prevalence of Obesity and Diagnosed Diabetes Among US Adults, 1991 and 2001

Mokdad, A. H. et al. JAMA 2003;289:76-79

1986 -> 2000. BMI > 30 2x; >40 4x; > 50 6x.

Relative Risk of Type 2 Diabetes in US Women According to BMI

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Relative Risk (age-adjusted)</th>
<th>Bars represent 95% confidence intervals</th>
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<tbody>
<tr>
<td>&lt;22.0</td>
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<td>22.0–22.9</td>
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<td>35.0</td>
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Plasma Glucose and Insulin Profiles After Oral Glucose Challenge


Non-Insulin Dependent Diabetes Mellitus

Affects 15% of Americans over the age of 60
Affects 100 million individuals worldwide
Treatment accounts for 10% of all health care expenditure in US

Complications include:
- Retinopathy
- Nephropathy
- Neuropathy
- Dyslipidemia
- Coronary artery disease
Definition of Type II Diabetes Mellitus

- Not absolutely dependent on exogenous insulin
- Absence of autoimmune destruction of beta cells
- Glycemia due to combined insulin resistance and relative beta cell failure
- Very common
  - 85% all diabetes
  - 5-7% of population
  - 15% of population > 60
- Most patients > 60 years old, but frequency increasing in young
- Strong genetic influence:
  - Near 100% concordance identical twins
  - 40% positive family history
- Strong environmental interaction: 50% males, 70% females are obese
- Male 3:2
Clinical definition of diabetes

Plasma glucose > **200 mg/dl** at any time
or
Fasting (post-absorptive) plasma glucose > **125 mg/dl**
or
2 hour post-75gm oral glucose load plasma glucose > **200 mg/dl**

Diab. Care; 23:381, 2000
Clinical Definition Impaired Glucose Tolerance

Fasting (post-absorptive) plasma glucose: 100-125 mg/dl
or
2 hr (OGTT) plasma glucose: 140 - 199 mg/dl

Diab. Care; 23:381, 2000 & update 4 04

Predisposing Genes
Predisposing Environment

Obesity

Type 2 Diabetes

80% diabetic are obese
50 % obese are diabetic
Figure 1

Note: Figures may be difficult to render in a web browser. In such cases, we recommend downloading the PDF version of this document.
In the absence of insulin, GLUT4 is localized to an intracellular compartment.

In the presence of insulin, GLUT4 translocates to the plasma membrane.

Diagram showing the localization of GLUT1 and GLUT4 in the absence and presence of insulin, along with the involvement of IRS, PI 3-K, AKT, PKC, and the translocation process.
Potential rate-controlling steps in insulin-mediated muscle glycogen synthesis

Obici et al. Nature Medicine. 8:1396, 2002
Mechanisms FFA-induced insulin resistance in skeletal muscle

Adipose tissue is an endocrine organ.
In obese mice, adipose tissue macrophages have an unusual morphology: lipid vacuoles, multinucleated.

Weisberg et al., JCI, Dec 2003

Adipose tissue macrophages

Perigonadal: \\
$r^2 = 0.7, P < 10^{-4}$

Perirenal: \\
$r^2 = 0.7, P < 10^{-4}$

Mesenteric: \\
$r^2 = 0.9, P < 10^{-4}$

Subcutaneous: \\
$r^2 = 0.39, P < 0.01$

Weisberg et al., JCI, Dec 2003
Improved insulin sensitivity in Ccr2-/- mice

- Ccr2 +/- with dietary obesity; 44% body fat
- Ccr2 -/- with dietary obesity; 45% body fat
Risk Factors for Type II Diabetes (II)

“Barker Hypothesis”

Low birth weight and slow 1st year growth lead to:

- Compromised beta cell development and increased insulin resistance
- “Thrifty phenotype”
- Insulin resistance
- Low protein intake, especially cysteine, results in decreased islet vascularity in the rat
Prospective Analysis
8 Year Cumulative Incidence (%) of Type 2 Diabetes in Pima Indians
317 NGT/62 Diabetics

Diabetes Prevalence (%) in Offspring by Mother’s Diabetes at Pregnancy
Longitudinal Study of the Transition from NGT to Type 2 Diabetes
Early Insulin Response vs Insulin Action

Adapted from Weyer et al, 1999
OBESITY-DIABETES

- CATASTROPHERS: SIEGE OF PARIS; WWI; WWII.
- MIGRATIONS: JAPAN ----> HAWAII
  INDIA ---- --> UNITED KINGDOM
  TAKELAU --> NEW ZEALAND
  PIMANS
- AMELIORATING EFFECTS OF WEIGHT LOSS
Percentage of Weight Loss Achieved Over the 2-Year Study Period (n = 60) and Individual Weight Measures at Baseline and at 2 Years

Age Adjusted Incidence Rates of NIDDM in Pima Indians by Body Mass Index and Parental NIDDM

PARENTAL DIABETES

INCIDENCE

New Cases/1000 Person-Years

0 20 40 60 80 100

<20 20-25 25-30 30-35 35-40 ≥40

Body Mass Index (kg/m²)

Adiposity(u) = f(Q) − f(W)

Past

Present

Phenotype

Genotype

Famine (IQ)

Hurt (W)

Adiposity

Feast (IQ)

Sitting (W)

Phenotype

Genotype

Adiposity
Kahn SE et al. Nature 2006
Diabetes-susceptibility QTLs

**Diabetes-susceptible strains**
- C57BL/KsJ
- DBA/2J
- SWR/J
- C3H.SW/SnJ
- C3HeB/FeChp (males only)
- CBA/L1 (males only)

**Diabetes-resistant strains**
- C57BL/6J
- 129/J
- Ma/MyJ
Do beta cells in D/D animals replicate as well as beta cells in B/B animals?
Zebrafish


prior candidates

TCF2, SLC30A8 not on this affy array

[11C] DTBZ and PET visualizes the human pancreas

<table>
<thead>
<tr>
<th>Gene variants</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>PPARG (P11A)</td>
<td>Alimi et al., 2008</td>
</tr>
<tr>
<td>PPARG (G48R)</td>
<td>Baron, Diabetologia, 2008</td>
</tr>
<tr>
<td>ECN321 (K235K)</td>
<td>Gluca, Diabetes, 2004</td>
</tr>
<tr>
<td>CAPN9 (SNP 134 G allele)</td>
<td>Wendum, Diabetes, 2003</td>
</tr>
<tr>
<td>PKN13 (SNP)</td>
<td>Wendum, Diabetes, 2006</td>
</tr>
<tr>
<td>LTPY (K110Q)</td>
<td>Qi, Human Molecular Genetics, 2008</td>
</tr>
<tr>
<td>ZEA (C491G)</td>
<td>Cauchi, current study, 2007</td>
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<td>CLP7-2 (c793146 T allele)</td>
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Odds Ratio (T2D)