Etiology and genetics of type 2 diabetes

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Definition of Diabetes Mellitus

- a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both.
**Type 2 Diabetes** – due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance

- may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance

**Type 1 Diabetes** – due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency
Natural History of Type 2 Diabetes

<table>
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<th>Normal</th>
<th>IGT</th>
<th>Type 2 diabetes</th>
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<td>Insulin resistance</td>
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<td>Insulin secretion</td>
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<tr>
<td>Blood glucose</td>
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Time

Pathogenesis of Type 2 diabetes

Genetic Factors
- Insulin secretion genes
- Beta-cell capacity genes
- Insulin resistance genes
- Obesity genes etc.

Environmental Factors
- Obesity
- Physical inactivity/ Age
- Diet
- Environmental toxin? etc.

Type 2 DM
- Failing insulin secretion
- Glucose desensitization of beta-cell
- Increased insulin secretion
- Decreased insulin sensitivity

C. Ronald Kahn 2001
Principles and Practice of Endocrinology and Metabolism, 3rd ed.
Type 2 Diabetes: Genetic Disease

- Concordance rate in identical twins: 70 - 90%.
- Individuals with a parent with type 2 DM have an increased risk of diabetes: If both parents have type 2 DM, the risk in offspring may reach 40%.
- Ethnic differences in the prevalence of T2D
- Polygenic and multifactorial
  - Environmental factors such as obesity, nutrition or physical inactivity modulate phenotype.
Searching Genes for Type 2 Diabetes

• Began over 4 decades ago with cloning of human insulin
• Candidate gene studies for insulin action and insulin secretion and family linkage studies
• “Diabetes Mellitus — A Geneticist’s Nightmare”

Type 2 diabetes
• Is genetically heterogeneous
• Is almost certainly polygenic
• Strong gene/gene and gene/environmental interactions play important roles in development of type 2 diabetes
Genes confirmed to be involved in T2D risk

Genomewide association study
Common Genetic Variants of T2DM and Their Suggested Function

- **Insulin Secretion**
  - β-cell Dysfunction
    - THADA (Simonis-Bik et al., 2010)
    - ADCY5 (Dupuis et al., 2010)
    - IGF2BP2 (Groenewoud et al., 2008)
    - WFS1 (Sparso et al., 2008)
    - DGKB (Ingelsson et al., 2010)
    - JAZF1 (Grarup et al., 2008)
    - GCK (Ingelsson et al., 2010)
    - SLC30A8 (Kirchhoff et al., 2008)
    - CDC123/ CAMK1D (Grarup et al., 2005)
    - TCF7L2 (Kirchhoff et al., 2008)
    - KCNQ1 (Tan et al., 2009)
    - KCNJ11 (Nielsen et al., 2003)
    - CENTD2 (Voight et al., 2010)
    - MTNR1B (Lyssenko et al., 2009)
    - TSPAN8/ LGR5 (Grarup et al., 2008)
    - C2CD4A (Ingelsson et al., 2010)
    - GIPR (Ingelsson et al., 2010)
    - ANK1 (Morris et al., 2012)
  - β-cell Development
    - PROX1 (Ingelsson et al., 2010)
    - CDKAL1 (Groenewoud et al., 2008)
    - GLIS3 (Yang et al., 2011)
    - CDKN2A/B (Pascoe et al., 2007)
    - HHEX/IDE (Pascoe et al., 2007)
    - HNF1A (TCF1) (Harries et al., 2006)
    - HNF1B (TCF2) (Haumaitre et al., 2008)
    - HNF4A (Wang et al., 2000)

- **Insulin Resistance**
  - Obesity
    - GRB14 (Heid et al., 2010)
    - KLF14 (Small et al., 2011)
    - SPRY2 (Kilpelainen et al., 2011)
    - FTO (Frayling et al., 2007)
    - MC4R (Loos et al., 2008)
  - Insulin Action
    - GCKR (Dupuis et al., 2010)
    - IRS1 (Kilpelainen et al., 2011)
    - PPARG (Altshuler et al., 2000)
    - ADAMTS9 (Simonis-Bik et al., 2010)
    - ANKRD55 (Morris et al., 2012)

- **Unknown**
  - NOTCH2 (Grarup et al., 2008)
  - BCL11A (Voight et al., 2010)
  - RBMS1 (Qi et al., 2010)
  - UBE2E2 (Yamauchi et al., 2010)
  - ST6GAL1 (Kooner et al., 2011)
  - MAEA (Cho et al., 2012a)
  - ZBED3 (Voight et al., 2010)
  - ZFAND3 (Cho et al., 2012a)
  - KCNK16 (Cho et al., 2012a)
  - GCC1 (Cho et al., 2012a)
  - TP53INP1 (Voight et al., 2010)
  - PTPRD (Tsai et al., 2010)
  - TLE4 (Voight et al., 2010)
  - TLE1 (Morris et al., 2012)
  - VPS26A (Kooner et al., 2011)
  - ZMIZ1 (Morris et al., 2012)
  - DUSP8 (Kong et al., 2009)
  - CCND2 (Morris et al., 2012)
  - KLHDC5 (Morris et al., 2012)
  - HMG20A (Morris et al., 2012)
  - ZFAND6 (Voight et al., 2010)
  - AP3S2 (Kooner et al., 2011)
  - PRC1 (Voight et al., 2010)
  - CILP2 (Morris et al., 2012)
  - PEPD (Cho et al., 2012a)
  - SRR (Tsai et al., 2010)
  - BCAR1 (Morris et al., 2012)

Kwak SH, Park KS, Arch Pharm Res 2013
Integration of Environmental Factors with Genetic Informations...

- Has potential to clarify the roles of both environment and genotype in disease causation.

Increased prevalence of diabetes
Environmental factors

- Westernized diet
- Physical inactivity
- Obesity
- Environmental pollutants
- Drugs etc.
Obesity and Diabetes/Insulin Resistance

2.5 million years → 50 years
Body fat and insulin resistance

- Insulin sensitivity and body fat percentage
  - Linear correlation: $r = -0.50$, $p < 0.0001$

- Insulin sensitivity and body mass index (BMI) for males and females
  - Males: $r = 0.59$, $p < 0.05$
  - Females: $r$ not reported

- Intramyocellular lipid (IMCL) and insulin sensitivity
  - Linear regression: $r = 0.88$, $p = 0.0001$

- Intra-abdominal fat area and insulin sensitivity index
  - Linear regression with $r$ not reported
Increased FFA availability and Insulin Resistance

- Glucose
  - $\text{G-6-P} 
  - Pyruvate

- Acetyl CoA
  - NADH
  - NAD$^+$

- IRS-1/IRS-2 serine/threonine phosphorylation
  - IRS-1/IRS-2 tyrosine phosphorylation

- PI 3 kinase
  - PKC$\theta$

- GLUT4

- Plasma glucose
  - Insulin
  - Fatty acid

- Fatty acyl CoA
  - Diacylglycerol
  - Ceramides

- Serine/threonine Kinase cascade
Adipokines for diabetes, metabolic syndrome and atherosclerosis

Genetic factors
Variations of adipokine genes

Environmental factors
Causing obesity
- Adipocyte differentiation
- ROS
- Mitochondrial dysfunction
- ER stress

Alterations in Adipokines expression
- Lipoprotein lipase
- IL-6
- hsCRP
- TNFα
- Adipsin
  (Complement D)
- Adiponectin
- Plasminogen activator inhibitor-1 (PAI-1)
- Resistin
- Insulin
- Leptin
- FFA
- RBP4

Insulin resistance
Diabetes mellitus

Atherosclerosis
Persistent organic pollutants (POPs) and diabetes

Interaction between waist circumference and serum concentrations of OC pesticides on the prevalence of insulin resistance

Adjusted Odds ratio

Lee DH et al. Diabetes Care 2007
Environmental factors for beta cell dysfunction

Islet pathology of type 2 diabetic patients

Amyloid deposition

Hyaline degeneration of the islands of Langerhans

Pictures are from N Engl J Med 2000; 343: 411-419
Gluco-/lipotoxicity and inflammation of beta cells

High glucose
- Oxidative stress
  - TRX/TXNIP
  - IL-1β
- Inflammation
  - CCL2
  - CCL3
  - CXCL8

High FFA
- Ceramide
- Long chain acyl CoA
- Diacylglycerol
  (cytotoxic)

Pdx1
MafA
Insulin gene

Transcription
The incretin effect is reduced in Type 2 Diabetes

Control Subjects

Patients With Type 2 Diabetes

*ps.05 compared with respective value after oral load.
mitochondrial dysfunction in the pathogenesis of diabetes mellitus

Impaired insulin secretion

β cell

Target tissue

↓ Biological effects

Insulin resistance

Maechler P and Wolheim CB. Nature 2001

Mitochondrial dysfunction
As a unifying pathophysiological defect

Lowell BB and Shulman GI: Science 2005
Gene to environment interaction

Type 2 Diabetes

Genetics

Environment
- Age
- Obesity and nutrients
- Exercise
- Intrauterine environment

Epigenetics
- DNA methylation
- Histone modifications
- microRNAs
Thrifty phenotype

Maternal malnutrition (? Protein deficiency)

Fetal malnutrition

Insulin resistance
Inherited (genetic)
Obesity
Ageing

Skeletal muscle
Predisposition to insulin resistance

Beta cell
Impaired insulin secretion in adult

Other tissues
Hypertension*
Dyslipidemia*
Hypercoagulability*

Glucose intolerance*

> Type 2 Diabetes*

* Indicates features of metabolic syndrome

Barker et al. BMJ, 1992
Epigenetic changes during development of T2DM

Pinney and Simmons 2010
**PGC-1α promoter is hypermethylated in T2DM patients**

Barres et al. Cell Metab 2009
Scheme of pathogenesis of T2DM

Prokopenko et al. 2008
Metabolic characteristics of Type 2 Diabetes in Korean

- Nonobese
- Lower insulin secretory capacity
- Less insulin resistance

Comparison of plasma insulin response to oGTT between Caucasian and Korean

Reaven, Diabetologia 1989

K-U Lee et al, 1994

Insulin sensitivity of T2 DM in Korea
Limited beta-cell capacity (Genetic factors, malnutrition)

Insulin resistance (life-style changes, obesity)

Accelerated beta-cell decompensation

Non-obese T2DM
longitudinal changes in β-cell function and insulin sensitivity in development of T2DM in Korean

- Ansung(rural)
  - Population: 135,000
  - Age: 40-69 yr
  - Subject: 5,024
- Ansan(Urban)
  - Population: 550,000
  - Age: 40-69 yr
  - Subject: 5,014

Biennial FU with Detailed Clinical and Biochemical Information

- Genetic Information
- Anthropometric parameters
- Demographic parameters
- Biochemical parameters

UK : Whitehall II study
Lancet 2009

Korean : Ansung–Ansan study
Lancet Diabetes Endocrinology 2016

**Insulin sensitivity**

- **UK : Whitehall II study**
  - HOMA2-%S
  - Time until end of follow-up (years)
  - Non-diabetics: 2927, 65, 84, 25, 1472, 2115, 50, 143, 90, 138, 3366, 274, 1, 239
  - Incident diabetes: 42, 43, 59, 41, 10, 18, 60, 120, 94, 43, 6, 60, 41, 164
  - Decrease by 34.2%

- **Korean : Ansung–Ansan study**
  - HOMA2-%S
  - Time until end of follow-up (years)
  - NGT: Decrease by 20%
  - Diabetes: Decrease by 30%

**Insulin secretion**

- **UK : Whitehall II study**
  - HOMA2-%B
  - Time until end of follow-up (years)
  - Non-diabetics: 2927, 65, 84, 25, 1472, 2115, 50, 143, 90, 138, 3366, 274, 1, 239
  - Incident diabetes: 42, 43, 59, 41, 10, 18, 60, 120, 94, 43, 6, 60, 41, 164
  - Increase by 10.5%

- **Korean : Ansung–Ansan study**
  - HOMA2-%B
  - Time until end of follow-up (years)
  - Decrease by 30%
Type 2 diabetes

Impaired glucose tolerance

Beta cell dysfunction

Insulin resistance / Hyperinsulinemia

Genetic susceptibility

Environmental factors

Korean

Genetic susceptibility

Beta cell dysfunction

Environmental factors

Insulin resistance

Impaired glucose tolerance

Type 2 diabetes

Obese

Nonobese
Genetic susceptibility of type 2 diabetes in Korean (common variants)

**Trans-ethnic common genes**

- **Allele frequency**
- **Number of variants**

**Korean(Asian) specific genes**

- **UBE2E, C2CD4A-C2CD4B**
- **GLIS3, PEPD, FITM2-R3HDL-M-HNF4A, KCNK16, MAEA, GCC1-PAX4, PSMD6 and ZFAND3. GLIS3**

- **16189 T>C variant**
  - **Diabetologia 2008**

- **mtDNA haplogroup**
  - **Nature Genetics 2011**
  - **Am J Hum Genet 2007**
Pathophysiology of type 2 diabetes mellitus – balanced view

- Genetically determined beta cell function/mass
  - Amyloid deposition
  - Inadequate stimulation by incretin
  - Cytokines
  - Malnutrition in utero
  - Mitochondrial dysfunction
  - Lipotoxicity

- Genetically determined insulin action
  - Obesity-FFA, adipokines
  - Physical inactivity
  - Aging
  - Drug
  - Malnutrition in utero
  - Mitochondrial dysfunction

Mild Hyperglycemia

Type 2 Diabetes

Beta cell dysfunction

Insulin Resistance

Glucose toxicity