Pathophysiology of Asian Diabetes

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Seoul National University College of Medicine
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
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 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.

Type 2 diabetes
- A Geneticist’s Nightmare”
Common Genetic Variants of T2DM and Their Suggested Function

Kwak SH, Park KS, Arch Pharm Res 2013
Environmental factors

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

2.5 million years

50 years
Body fat and insulin resistance

Insulin sensitivity

**Intramyocellular lipid**

Diabetes. 1993;42:1663-1672

Obesity Res. 1995:3(suppl 2):179S-186S;

Diabetes. 1993;42:1663-1672
Increased FFA availability and Insulin Resistance

Glucose $\rightarrow$ G-6-P $\rightarrow$ Pyruvate $\rightarrow$ Acetyl CoA + NADH

- HK
- PFK
- PDH

Glucose $\rightarrow$ Insulin

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

PI 3 kinase $\rightarrow$ PKC

Increased FFA availability and Insulin Resistance
Obesity and diabetes – role of adipokines

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
↑ Agiotensinogen
↑ Insulin
↑ FFA
↑ Resistin
↑ Leptin
↑ RBP4
↑ Plasminogen activator inhibitor-1 (PAI-1)

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

Park W-H et al.
Biofactors 2013
Environmental factors for beta cell dysfunction

Gluco-/lipotoxicity and inflammation of beta cells

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

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

Pdx1, MafA
Insulin gene transcription

Inflammation
The incretin effect is reduced in Type 2 Diabetes

Control Subjects

Insulin (mU/L)

Time (min)

Patients With Type 2 Diabetes

Insulin (mU/L)

Time (min)

* ps.05 compared with respective value after oral load.

Gene to environment interaction

Type 2 Diabetes

Genetics

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

Epigenetics
- DNA methylation
- Histone modifications
- microRNAs
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*

Atherogenesis*

Type 2 Diabetes*

*Barker et al. BMJ, 1992

* Indicates features of metabolic syndrome
Asian Diabetes phenotype
People in Asia develop diabetes with a lesser degree of obesity than those in other regions

A

<table>
<thead>
<tr>
<th>Prevalence (%)</th>
<th>Obesity BMI &gt;= 30 kg/m²</th>
<th>Overweight BMI &gt;= 25 kg/m²</th>
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<tbody>
<tr>
<td>USA</td>
<td>[Prevalence data]</td>
<td>[Prevalence data]</td>
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<tr>
<td>India</td>
<td>[Prevalence data]</td>
<td>[Prevalence data]</td>
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The South Asian ("Asian Indian") phenotype

In spite of lower BMI, South Asians have

- More insulin resistance and hyperinsulinemia
- More abdominal fat
- Higher level of CRP
- Lower levels of adiponectin
- Characteristic dyslipidemia
  - Low HDL
  - High TG
  - High small dense LDL
- Increased susceptibility to T2D and CAD

East Asian phenotype

- Lower BMI
- Less insulin resistance
- Lower insulin secretory capacity

Comparison of plasma insulin response to OGTT between Caucasian and Korean

Insulin sensitivity of T2 DM in Korea

Insulinogenic Index

C HOMA-IR

UK: Whitehall II study
Lancet 2009

Korean: Ansung-Ansan study
Lancet Diabetes Endocrinology 2016

Insulin sensitivity
-34.2%

Insulin secretion
+10.5%

NGT
-20%

diabetes
-30%

years before diabetes onset
Type 2 diabetes

Impaired glucose tolerance

Beta cell dysfunction

Insulin resistance / Hyper-insulinemia

Genetic susceptibility

Environmental factors

Obese

Type 2 diabetes

Impaired glucose tolerance

Beta cell dysfunction

Insulin resistance

Genetic susceptibility

Environmental factors

Nonobese

Caucasian

Korean
# Metabolic phenotypes of T2DM in Korean

<table>
<thead>
<tr>
<th>Metabolic Phenotype</th>
<th>Insulin Sensitivity</th>
<th>Insulin Secretion</th>
<th>Diabetes (%)</th>
<th>PAF (%)</th>
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</thead>
<tbody>
<tr>
<td>High Insulin sensitivity &amp; High Insulin secretion</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td>19%</td>
<td>&lt;0.05</td>
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<tr>
<td>Low Insulin sensitivity</td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
<td>21%</td>
<td>3.5% (12.1)</td>
</tr>
<tr>
<td>Low Insulin secretion</td>
<td><img src="image5.png" alt="Graph" /></td>
<td><img src="image6.png" alt="Graph" /></td>
<td>47%</td>
<td>12.1 (7.5-14.9)</td>
</tr>
<tr>
<td>Low Insulin sensitivity &amp; Low Insulin secretion</td>
<td><img src="image7.png" alt="Graph" /></td>
<td><img src="image8.png" alt="Graph" /></td>
<td>13%</td>
<td>36.7 (29.5-41.4)</td>
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</tbody>
</table>

*PAF: population attributable fraction*
Genetic susceptibility of type 2 diabetes in Korean

### Trans-ethnic common genes

- UBE2E, C2CD4A-C2CD4B
- GLIS3, PEPD, FITM2-R3HDML-HNF4A, KCNK16, MAEA, GCC1-PAX4, PSMD6 and ZFAND3. GLIS3

### Korean(Asian) specific genes

- Voltage gated potassium channel KCNQ1
- 16189 T>C variant
- mtDNA haplogroup

References:
- Nature Genetics 2008
- Am J Hum Genet 2007
- Diabetes 2008
- Nature Genetics 2010
- Diabetologia 2008
- Nature Genetics 2011
PAX4 variants as Asian specific functional variants

- Whole exome study of Korean

PAX4 (Paired Box 4)
- Transcription Factor Involved in Pancreatic Islet Development
- rs2233580 R192H: OR 1.66 (MAF 8%)
- rs3824004 R192S: OR 1.80 (MAF 4%)
- Asian specific variants:
  - associated with younger age of onset, low C-peptide level

PAX4 192 Codon Variation

Effect of PAX4 variants on glucagon promoter suppression

Possible Amino Acid Changes
- Arg, Arg, Arg, His, Ser, Arg, Ser, His

LD measure for two SNPs: R-sq 0.002, D'=0.619

Human glucagon promoter

<table>
<thead>
<tr>
<th>CHR</th>
<th>SNP1</th>
<th>SNP2</th>
<th>HAPLOTYPE</th>
<th>AA</th>
<th>Group</th>
<th>Frequency</th>
<th>OR</th>
<th>P</th>
<th>Overall P</th>
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<tr>
<td>7</td>
<td>rs2233580</td>
<td>rs3824004</td>
<td>ACG</td>
<td>Arginine</td>
<td>Positive Charge</td>
<td>0.874</td>
<td>0.57</td>
<td>2.53E-09</td>
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<tr>
<td>7</td>
<td>rs2233580</td>
<td>rs3824004</td>
<td>ATG</td>
<td>Histidine</td>
<td>Positive Charge</td>
<td>0.000</td>
<td>1.66</td>
<td>1.11E-05</td>
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<tr>
<td>7</td>
<td>rs2233580</td>
<td>rs3824004</td>
<td>ACT</td>
<td>Serine</td>
<td>Polar Uncharged</td>
<td>0.044</td>
<td>1.00</td>
<td>8.00E-01</td>
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<tr>
<td>7</td>
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<td>rs3824004</td>
<td>ATT</td>
<td>Asparagine</td>
<td>Polar Uncharged</td>
<td>0</td>
<td>-</td>
<td>-</td>
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</table>
Nonsynonymous Variant in GLP1R and Decreased Risk of T2D and CVD

- GLP1R p.Arg131Gln associated with decreased risk of T2D in Koreans with **OR 0.84 (0.80 - 0.90)**
- Common in East Asians (MAF 0.23), and South Asians (MAF 0.11)
- Mainly expressed in pancreatic β-cells but also in cardiac muscle, hypothalamus, and stomach
- 7 Transmembrane G protein coupled receptor

### Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Arginine</th>
<th>Glutamine</th>
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</thead>
<tbody>
<tr>
<td>Polarity</td>
<td>Positively Charged</td>
<td>Polar Uncharged</td>
</tr>
<tr>
<td>pH</td>
<td>Basic</td>
<td>Neutral</td>
</tr>
<tr>
<td>Residue weight</td>
<td>156</td>
<td>128</td>
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<tr>
<td>Secondary structure propensity</td>
<td>α indifferent</td>
<td>α former</td>
</tr>
</tbody>
</table>

### Association of GLP1R Nonsynonymous Variants With CVD (N = 1,496)

<table>
<thead>
<tr>
<th>Gene</th>
<th>HGVS (rsID)</th>
<th>CVD Cases</th>
<th>CVD Controls</th>
<th>CVD Cases AF</th>
<th>CVD Controls AF</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAX4</td>
<td>p.Arg192His (rs2233580)</td>
<td>239</td>
<td>1257</td>
<td>0.125</td>
<td>0.096</td>
<td>1.30 (0.95 - 1.78)</td>
<td>0.100</td>
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<tr>
<td>GLP1R</td>
<td>p.Arg131Gln (rs3765467)</td>
<td>239</td>
<td>1257</td>
<td>0.159</td>
<td>0.199</td>
<td>0.77 (0.59 - 0.99)</td>
<td>0.041</td>
</tr>
</tbody>
</table>
Risk factors for type 2 diabetes

- Conventional risk factors
  - Age
  - Obesity
  - Sedentary life style
  - Dietary factors
  - Family history of diabetes
  - Gestational diabetes
  - PCOS, hypertension, dyslipidemia, metabolic syndrome.....

- Emerging risk factors
  - Decreased sleep
  - Drug-induced metabolic changes
  - Environmental pollutants
  - Low birth weight and fetal malnutrition
  - others
Pathogenesis of T2DM

Susceptibility

Genetic factors
- Normal Insulin sensitivity & Insulin secretion (19%)
- Insulin resistance only (21%)
- Decreased Insulin secretion only (47%)
- Insulin resistance & Decreased Insulin secretion (13%)

Environmental factors
- Obesity
- Physical inactivity
- Aging
- Drugs
- EDC

Progression

Clinical outcome

Lifestyle risk factors
- Epigenetic changes
- Changes in protein, lipid and metabolites
- Changes in microbiomes
Thank you for your attention