Type 2 diabetes via β-cell dysfunction in East Asian people

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The pathophysiology of type 2 diabetes mellitus
Blood glucose levels are the result of the balance between β-cell function and insulin resistance.
Transition from NGT to Diabetes

Adapted from Festa A et al. Diabetes 2006:55;1116
β-cell Function is a Major Contributor to Glucose Tolerance in Four Ethnic Groups in US

Adapted from ADA GENNID Study Group. Diabetes 2002:51;2170-2178
Insulin Secretory Dysfunction and Insulin Resistance in the Pathogenesis of Korean Diabetes Mellitus

Insulinogenic index

HOMA-IR

Dong J. Kim et al., Metabolism 2001:50(5);590-593
Standardized β-cell Function Decline over Insulin Resistance in Korean Diabetes

Insulinogenic index / HOMA-IR
The differences between Asians & Caucacians
Age-adjusted ethnic prevalence of diabetes mellitus in Hawaii in 1958–1959

<table>
<thead>
<tr>
<th>Race (single)</th>
<th>Number screened</th>
<th>Diabetes rate (per 1,000 persons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>4,473</td>
<td>7.3</td>
</tr>
<tr>
<td>Chinese</td>
<td>3,755</td>
<td>14.6</td>
</tr>
<tr>
<td>Filipino</td>
<td>4,321</td>
<td>21.8</td>
</tr>
<tr>
<td>Japanese</td>
<td>16,134</td>
<td>20.1</td>
</tr>
<tr>
<td>Korean</td>
<td>539</td>
<td>19.7</td>
</tr>
<tr>
<td>Hawaiian</td>
<td>626</td>
<td>48.8</td>
</tr>
</tbody>
</table>

Difference of Prevalence of Diabetes by Ethnicity

**Women**

- South Asian: 22.0%
- Chinese: 24.0%
- Black: 26.0%
- White: 30.0%

**Men**

- South Asian: 21.6%
- Chinese/Black: 26.0%
- White: 30.0%

**Diabetes Prevalence (%)**

**Body Mass Index (kg/m²)**

- Age-adjusted associations between diabetes prevalence and adiposity (body mass index, BMI)
- A BMI of 24 for Chinese women and a BMI of 26 for Chinese men are equivalent to a BMI of 30 for Caucasians.

Study design: UK Biobank recruited 502,682 U.K. residents aged 40–69 years. Researchers used baseline data on the 490,288 participants from the four largest ethnic subgroups: 471,174 (96.1%) white, 9,631 (2.0%) South Asian, 7,949 (1.6%) black, and 1,534 (0.3%) Chinese.

β-cell function and insulin resistance in four racial groups according to glucose metabolism status

Study design: Researchers identified studies that measured the insulin sensitivity index (SI) and acute insulin response to glucose (AIRg) in three major ethnic groups: Africans, Caucasians, and East Asians. Researchers identified 74 study cohorts comprising 3,813 individuals (19 African cohorts, 31 Caucasian, and 24 East Asian). Researchers calculated the hyperbolic relationship using the mean values of SI and AIRg in the healthy cohorts with normal glucose tolerance.
Reduced early-phase insulin secretion in East Asian compared with Caucasian individuals

Decreased Insulin Secretion in Japanese

Compensatory insulin secretion is lower in Japanese subjects with IGT or T2DM relative to Caucasian counterparts.

Study design: A total of 120 Japanese and 150 Caucasians were enrolled to obtain comparable distributions of high/low BMI values across glucose tolerance states (normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes), which were assessed by oral glucose tolerance tests. BMI in the two cohorts was distributed around the two regional cutoff values for obesity.

Body Composition Is the Main Determinant for the Difference in Type 2 Diabetes Pathophysiology Between Japanese and Caucasians

Jonas B. Møller, Takashi Kadowaki et al. Diabetes Care Volume 37, March 2014
Long-term prospective observational cohort studies, UK & South Korea
B-cell Dysfunction in East Asian type 2 Diabetes Mellitus

Long-term (10 years) prospective cohort studies investigating the trajectories of NGT to T2DM

- South Korea
  - initial decreased β-cell function

- United Kingdom
  - initial decreased insulin sensitivity

are prerequisites for the development of T2DM

Baseline characteristics of incident diabetes and non-diabetics cases - analysis from the Whitehall II study in UK

<table>
<thead>
<tr>
<th></th>
<th>Incident diabetes (N=505)</th>
<th>Non-diabetics (N=6033)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.1 (6.6)</td>
<td>52.6 (7.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Male</td>
<td>66%</td>
<td>71%</td>
<td>0.029</td>
</tr>
<tr>
<td>White</td>
<td>80%</td>
<td>92%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>28.18 (4.99)</td>
<td>25.60 (3.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.71 (0.91)</td>
<td>5.21 (0.47)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2-h postload glucose (mmol/L)</td>
<td>7.06 (2.48)</td>
<td>5.38 (1.42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>73 (30)</td>
<td>47 (30)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

| HOMA2-%S                | 103.4 (58.8%)             | 145.1% (63.2%)         | <0.0001 |
| HOMA2-%B                | **88.5 (39.0%)**          | **78.4% (30.3%)**      | <0.0001 |

β-cell function and insulin sensitivity in the development of type 2 diabetes
- a community-based 10 years prospective cohort study in South Korea

East Asians might have **reduced β-cell reserve capacity** that makes them **readily susceptible** to a minor decline of insulin sensitivity

A recent meta-analysis of East Asian studies has discovered eight novel loci for T2D, several of which showed suggestive associations in European populations.

Most of these variants are predicted to influence the risk of T2D by affecting insulin secretion.

The majority of loci reported to be associated with T2D show similar effect sizes in East Asian and European populations.

Comparison of effect sizes of type 2 diabetes risk in East Asians and Europeans for 53 confirmed single nucleotide polymorphisms
Characteristics of T2DM in East Asians

Comparing Asian and Caucasian people with type 2 diabetes, Asian patients would be characterized by:

- Lower BMI
- Higher amounts of visceral fat with a given BMI, waist circumference
- Predominant insulin secretory defect that might be explained by:
  - Lower β-cell mass & function
  - Genetic difference

Kim YG et al. Diabetologia 2013;56:696-708
BMI is not useful for comparison across ethnicity

The Y files: John Yudkin (L) and Chittaranjan Yajnik (R) share the same body mass index, but Yajnik’s body harbors significantly more fat.
Indian Diabetes is different from Diabetes in UK

The physical phenotype of US type 2 diabetes in 200 years ago was nearly similar with the phenotype of East Asian type 2 diabetes nowadays.

The fundamental pathophysiologies of type 2 diabetes are nearly the same.

The delicate differences observed between these races would be the temporary, transient phenomenon.

Dr. Peter H. Bennett, via personal communications 1996
Summary & Conclusion

On regarding the East Asian T2DM patients,

1. East Asians might have reduced \( \beta \)-cell reserve capacity
2. \( \beta \)-cell dysfunction, as the primary defect in T2DM development
3. Fundamental pathophysiologic mechanism of T2DM is similar in the East Asians and Caucacians