Overview of Type 2 diabetes and Prediabetes
Classification of Diabetes

- Type 1 (a) & (b)
- Type 2
- Other specific types
  - Hormones; drugs; liver disease; muscle disorders; pancreatitis; iron overload syndromes
- Gestational
Type 2 diabetes

- Genes
  - Impaired insulin secretion
- Environment
- Genes
  - Insulin Resistance

- Elevated glucose
Risk for developing type 2 diabetes

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Background population</td>
<td>10%</td>
</tr>
<tr>
<td>Average risk for siblings</td>
<td>30-40%</td>
</tr>
<tr>
<td>One parent with T2D</td>
<td>30-40%</td>
</tr>
<tr>
<td>Both parents with T2D</td>
<td>50-80%</td>
</tr>
<tr>
<td>Monozygotic twins</td>
<td>50-90%</td>
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</table>
Genome wide study - SNPs

- non coding region near CDKN2A/CDKN2B,
- intron of IGF2BP2
- Intron of CDKAL1
- Intron of TCF7L2
- SLC30A8 (Zinc transporter)
- HHEX
- PPARG
- KCNJ11
- FTO
- MC4R
Incidence of diabetes according to TCF7L2 allele in the DPP cohort

Florez et al NEJM 2006; 355:241
Prevalence of obesity

Prevalence of age adjusted rates of diabetes

Effect of obesity on glucose & insulin

Golay et al. JCEM 63: 481 (1986)
Type 2 diabetes

Genes → Impaired insulin secretion → elevated glucose

Environment → Insulin Resistance

Genes
Swedish obesity study – bariatric surgery prevent development of diabetes [1402 controls; 1489 surgery patients]
Prevalence of type 2 diabetes in Pima Indians in Sonora, Mexico and Arizona, USA

<table>
<thead>
<tr>
<th></th>
<th>Non-Pima Mexicans</th>
<th>Mexican Pima</th>
<th>US Pima</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI:</strong></td>
<td>24 - 27</td>
<td>24-26</td>
<td>33 - 35</td>
</tr>
<tr>
<td><strong>Physical activity:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mexican Pima</td>
<td>22 to 33 hr/wk</td>
<td></td>
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<tr>
<td>US Pima</td>
<td>2 to 12 hr/wk</td>
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</tbody>
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Mexican and US Pima genetically related

Schulz et al. Diabetes Care 2006; 29:1866
Identical twins who are discordant for obesity

Obese twin half as active
Obese twin under-report energy intake & over-report physical activity

Physical activity reduces the influence of genes on BMI and waist circumference

Naukkarinen et al 2012 Int J Obes 36:1017
Summary

• Type 2 diabetes affect 24 million people in the US

• Type 2 diabetes patients have a deficiency in insulin secretion and many also require higher amount of insulin to control their glucose levels (insulin resistance)

• The deficiency in insulin secretion is mostly due to genes

• The need for higher amounts of insulin (resistance) is genetic and environmental

• Obesity is the main environmental factor for resistance

• Reducing obesity rates will reduce rates of diabetes
Prediabetes – the high risk state for diabetes
Prediabetes is defined by test values that are higher than normal but lower than for the diabetes diagnosis

<table>
<thead>
<tr>
<th>Category</th>
<th>FPG</th>
<th>2hPG</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;100</td>
<td>&lt;140</td>
<td>&lt;5.7</td>
</tr>
<tr>
<td>IFG</td>
<td>100-125</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>IGT</td>
<td>---</td>
<td>140-199</td>
<td>---</td>
</tr>
<tr>
<td>High risk</td>
<td>----</td>
<td>----</td>
<td>5.7 - 6.5</td>
</tr>
<tr>
<td>DM</td>
<td>≥126</td>
<td>≥200</td>
<td>≥6.5%</td>
</tr>
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IFG – impaired fasting glucose; IGT – impaired glucose tolerance

2hPG – 2 hour glucose after 75 grams oral glucose

WHO cutoff for normal fasting plasma glucose is 110 mg/dl (6.1 mmol/l); & lower cutoff of 6% for HbA1c
A digression - What is HbA1c?

HbA1c measures the percentage of hemoglobin (the red stuff in your blood) that has an attached glucose molecule.

Normal glucose level — 4.3 to 5.6 % of hemoglobin has attached glucose — normal HbA1c

High glucose level — higher percentage of hemoglobin has attached glucose — higher HbA1c
Some facts about prediabetes

If you use the ADA defined test cutoffs:

• ~84 million (33.9%) of US adults; & ~48 % adults 65 and older have prediabetes

• ~2 % with people with pre-diabetes progress to diabetes every year (conversion rate varies by population characteristics and prediabetes definition)

• Prediabetes can convert back to normal – in one study from England, 86% became normal at 10 years
Diabetes prevention program (DPP) study - 3234 with FPG 95-125 + 2hPG 140-199 + overweight randomized to 7% weight loss + 150 mins exercise/wk or metformin or placebo

Figure 2. Cumulative Incidence of Diabetes According to Study Group.

Knowler et al NEJM 2002;346: 393
Conclusions from the DPP

• After an average of 2.8 yrs, lifestyle reduced incidence of diabetes by 58%

• On average, lifestyle intervention delayed the onset of diabetes by 3-4 years

• After 15 yrs follow-up, the cumulative incidence of diabetes was 55% in the lifestyle group; 56% metformin group; 62% placebo group
Before you embrace the prediabetes diagnosis

• You are labelling 1/3 of the adult US population as having an illness

• The DPP study used a high risk group (IGTT + IFG + overweight group). The benefits of intervention may not be as great in the general population

• Lack of evidence that prediabetes diagnosis prevents diabetes complications or premature death
Summary

• Prediabetes is defined by tests values that are higher than normal but lower than for the diabetes diagnosis

• What test and cutoffs you use can greatly affect who gets the diagnosis

• If you have prediabetes, weight loss and exercise can delay the onset of diabetes

• It is unclear that having the prediabetes label leads to better health
Treatment
Diabetes related complications:

- Stroke
- Eye disease
- Heart disease
- High blood pressure
- Kidney disease

Pain or amputation due to impaired blood flow

Peripheral neuropathy - pain; injury
UKPDS study

Per 1 % reduction in HbA1c:

- 37 % decrease in microvascular complications
- 14 % decrease in fatal & non-fatal MI

Stratton IM et al. BMJ 2000;321:405-412
Meta-analysis of 14 clinical trials of effects of exercise intervention (>8 wks) on HbA1c in type 2 DM

HbA1c 7.65% vs 8.31%; weighted mean difference (WMD) -0.66%; \( P<.001 \). No sig. difference in weight or BMI

_JAMA. 2001;286:1218-1227._
Randomized controlled study of gastric banding vs lifestyle weight loss in 60 obese patients (BMI 30 to 40) with DM for less than 2 years

Evidence based nutrition principles

- The total amount of carbohydrate in meals and snacks is more important than the source or the type.
- Replacing carbohydrates with monounsaturated fat reduces postprandial glucose spikes & triglycerides.
- You have to eat very large amounts of fiber to get the metabolic benefits.
- Limit saturated fats -- less than 10 % of energy intake.
- Dietary cholesterol intake – less than 300 mg/day.
1. Secretagogues (e.g. sulfonylureas)
2. Metformin
3. Alpha glucosidase inhibitors
4. Thiazolidinediones
5. GLP-1 receptor agonists
6. DPP-4 inhibitors
7. SGLT2 inhibitors
8. Pramlintide
9. Insulin
10. (Bromocriptine; colesevelam)
ADA/EASD algorithm 2015

6 classes of drugs:

- Metformin
- GLP1 receptor agonists/DPP 4 inhibitors
- Sulfonylureas (+other secretagogues)
- Pioglitazone
- SGLT2 inhibitors
- Insulin

In making therapeutic decision take into account efficacy; hypoglycemia risk; effect on weight; major side effects; cost
Overlap of phenotypes

Type 1

Type 2

Genetic syndromes
• 80 YO Hispanic woman
• Diagnosed 4 yrs ago routine testing
• HbA1 deteriorated from 7.4% to 13% within a year

On Metformin 1 gm BID Glyburide 5 mg daily

• GAD Ab >30 (1 or < U/mL)
• ICA 512 Ab 3.7 (<0.8 U/mL)