Type 2 diabetes: vascular complications at diagnosis

- 20–30% diabetic retinopathy
- 10–20% microalbuminuria
- 30–40% hypertension
- 50–80% dyslipidaemia

Macrovascular complications
- Microvascular complications

Natural History of Type 2 Diabetes

Adapted from Ramb-Hadad BA, Edelman SV. Risk factors. 1999 29:771-780
**Diabetes**

- Insulin resistance
- Insulin secretion
- Fasting glucose

**Pre-diabetes**

- Microvascular complications
- Macrovascular complications

**Overweight patient with visceral adiposity**

**Diabetes epidemic: 2003-2025**

- Global projections
- World 2003 = 194 million
- 2025 = 333 million
- Increase 72%

**Global projections for the diabetes epidemic: 2003-2025**

- 2003 = 194 million
- 2025 = 333 million
- Increase 72%

**The Thrifty Gene Hypothesis**

- Hunter-gatherer
- Modern society
- Energy storage for maximum metabolic efficiency
- Overloaded adipocyte
- Visceral obesity

**Survival**

- Famine
- Feast

**Inadequacy between our genes and the environment**
Pima Indians Thrifty Genes

The 10 Leading Countries for Diabetes Prevalence

Jean Vague (1948)

Jean Vague (1948)

Jean Vague (1948)

The evolving view of adipose tissue: an endocrine organ

Lyon CJ et al 2003
Adipose Tissue as Endocrine Cells

Angiotensinogen
Leptin
Adiponectin
TNF-α
IL-6
Adipsin (ASP)

Plasminogen activator inhibitor (PAI-1)

OVERLOADED VISCERAL ADIPOSE TISSUE BECOMES INSULIN RESISTANT

I am the culprit

OVERLOADED ADIPOCYTE

These amplifying signals increasingly impair adipocyte insulin signaling and eventually cause systemic insulin resistance in liver and muscles.

INSULIN RESISTANCE

Adverse cardiometabolic effects of products of adipocytes

Lipid metabolism, CVD

Hypertension

Atherogenic dyslipidaemia

Type 2 diabetes

Inflammation

Lipoprotein lipase

Insulin

FFA

Resistin

Lactate

Leptin

Adipsin (Compliment D)

Adiponectin

Plasminogen activator inhibitor-1 (PAI-1)

Atherosclerosis

Thrombosis

The inflammatory atherosclerotic process
Features of the Metabolic Syndrome

- Insulin Resistance
- Genetics
- Glucose Toxicity
- Other (??)
- Amylin (IAPP)
- Age
- Lipotoxicity (FFA, TG)
- Incretin Effect
- Hexosamines
- Beta Cell Failure
- TNF

Loss of early-phase insulin secretion in type 2 diabetes leads to harmful mealtime glucose spikes

Pattern of insulin secretion is altered early in type 2 diabetes

\[ \text{Pattern of insulin secretion is altered early in type 2 diabetes} \]

\[ \text{Loss of early-phase insulin secretion in type 2 diabetes leads to harmful mealtime glucose spikes} \]

\[ \text{Duration of daily glycaemic conditions in non-diabetics} \]

\[ \text{Duration of daily glycaemic conditions in non-diabetics} \]

\[ \text{Duration of daily glycaemic conditions in non-diabetics} \]
DECODE: risk for all-cause mortality

Adjusted for age, center, sex, cholesterol, body mass index (BMI), systolic blood pressure (SBP), smoking

Fasting plasma glucose (mg/dl)

<110 110–125 >126

140–199 <140

2-hour plasma glucose (mg/dl)

0.0 0.5 1.0 1.5 2.0 2.5

Hazard ratio

Adapted from DECODE Study Group. Lancet 1999;354:617–21

Hyperglycaemia: the role of oxidative stress?

Hyperglycaemia

Oxidative stress

Insulin resistance

Beta-cell

Endothelial dysfunction

Thrombosis

Need for early detection of type 2 diabetes and for a strict control of blood glucose in diabetic patients in order to avoid vascular events

Breakfast Lunch Dinner

Hyperglycaemia

Endothelium

Oxidative stress

Adhesion molecules

Atherosclerosis

Glucose Tolerance Categories

Diabetes Mellitus

IGT

Normal

FPG

2h PPQ (OGTT)

Diabetes Mellitus

IGT

Normal

AT LEAST THREE OF THE FOLLOWING

- Waist circumference
  - Men > 102 cm
  - Women > 88 cm
- Triglycerides = > 150 mg/dl
- HDL-Cholesterol
  - Men < 40 mg/dl
  - Women < 50 mg/dl
- Blood pressure = >130/ = >85 mm Hg
- Fasting glucose = >110 mg/dl

Clinical identification of the metabolic syndrome (IDF- April 2005)

**VISCERAL OBESITY**
- Waist circumference (ethnic specific)
  - Men > 94 cm
  - Women > 80 cm

  **AT LEAST TWO OF THE FOLLOWING**
  - Triglycerides > 150 mg/dl
  - HDL-Cholesterol
    - Men < 40 mg/dl
    - Women < 50 mg/dl
  - Blood pressure > 130/ = >85 mm Hg
  - Fasting glucose > 100 mg/dl

Waist circumference is a surrogate marker of visceral fat

**Women**

> 94 cm = Increased risk

**Men**

> 94 cm = Increased risk

IDF; 2005

**WAIST CIRCUMFERENCE - LEBANON**

<table>
<thead>
<tr>
<th>Waist Circumference</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 94 cm</td>
<td>34%</td>
</tr>
<tr>
<td>94 - 102 cm</td>
<td>31%</td>
</tr>
<tr>
<td>&gt; 102 cm</td>
<td>35%</td>
</tr>
<tr>
<td>&lt; 80 cm</td>
<td>32%</td>
</tr>
<tr>
<td>80 - 88 cm</td>
<td>26%</td>
</tr>
<tr>
<td>&gt; 88 cm</td>
<td>42%</td>
</tr>
</tbody>
</table>

**MEN (444)**

**WOMEN (415)**

**NATURAL HISTORY OF IGT**

- After 10 years
  - Normal: 33%
  - IGT: 33%
  - Diabetes: 33%

Can type 2 diabetes be prevented?

- Insulin Production
  - Hyperglycemia
  - IGT
  - IFG
  - Normal

**TRIGGERING**
- Genes & Environment
- Insulin Production

Goals behind treating pre-diabetes

- Avoiding β-cell dysfunction will allow a delayed progression from pre diabetes to diabetes
- Treating individuals at risk of developing diabetes will translate into improved CVD outcomes and mortality rate
PRE DIABETES INTERVENTIONAL TRIALS

• Lifestyle intervention
• Pharmacotherapy

Prevention of type 2 diabetes by lifestyle changes in 522 persons with IGT

Tuomilehto J et al. NEJM 2001;344:1343

Cumulative probability of remaining free of diabetes

Study year

Subjects at risk
Total no. 507 471 374 167 53 27
Cumulative no. with diabetes:
Intervention group 5 15 22 24 27 27
Control group 16 37 51 53 57 59

Prevention of Type 2 Diabetes
Pharmacotherapy for IGT

WOSCOPS: Effect of Pravastatin on Development of Diabetes

Pravastatin
Placebo

30% RRR
p<0.036


HOPE – onset of new diabetes

Ramipril
Placebo

Patients developing diabetes (%)
Follow-up (years)

Yusuf S. AHA 72nd Session, Atlanta, USA, November 1999.

LIFE: New-Onset Diabetes

Intention-to-Treat

Adjusted Risk Reduction 25 %, p<0.001
Unadjusted Risk Reduction 25 %, p<0.001

B. Dahlöf at the American College of Cardiology, Atlanta, GA, March 17-20, 2002.
Potential Underlying Mechanisms of Benefit

- Modulation of inflammatory cytokines
  - By reducing IL-6 & TNF-α, lipoprotein lipase activity is increased & lipolysis in adipose tissue decreased
  - Interruption of natural progression from central obesity to insulin resistance
- Improvement of endothelial function
  - Improved capillary recruitment & insulin resistance
  - Improved tissue perfusion & glucose & insulin transport
- Improvement of beta cell function
  - Decreased gluco and lipo toxicity
  - Decreased oxidative stress
  - Decreased beta cell apoptosis


Type 2 Diabetes Mellitus: the classical approach

- "chronic hyperglycemia suspected by the presence of excessive thirst and polyuria »
- Goals of management: avoid symptoms related to this hyperglycaemia

Type 2 Diabetes Mellitus: the new approach

- atherosclerotic vascular disease with a high blood glucose
- Goals of management: prevent, delay, arrest vascular complications

Le prédiabète est un état d'obésité viscérale et de l'insulinorésistance qui en découle
Le risque vasculaire est présent dès ce stade à cause de la sécrétion d'adipokines inflammatoires et pro-thrombotiques, et de la dyslipidémie et de l'hypertension, souvent déjà présentes
L'évolution vers l'hyperglycémie est un épiphanème qui dépend de la performance des cellules bêta

Le concept de syndrome métabolique ne doit pas être perçu comme:
- Une anomalie supplémentaire par rapport aux différents éléments qui le composent
- Un plus dans la prise en charge des désordres métaboliques

Mais comme
- Un moyen de dépister au plus tôt dans une population donnée les personnes à risque et leur proposer une prévention adéquate

Merci de votre attention