Obesity and Type 2 Diabetes Mellitus - the Epidemic

Dr M R Munday
UCL School of Pharmacy
University College London
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Type 1 Diabetes Mellitus, Juvenile Diabetes.
Absolute lack of insulin due to destruction of β cells in the Islets of Langerhans of pancreas that secrete insulin

Type 2 Diabetes Mellitus, Maturity Onset Diabetes.
Insulin resistance of peripheral tissues and impaired insulin secretion
- This form is very closely related to/ caused by OBESITY

Diabetes Mellitus is characterized by high plasma glucose concentration.
Glucose chemically attaches to proteins and affects protein shape and function

eg. glycosylated haemoglobin (hA1c) has reduced ability to carry oxygen
microvascular disease eg thickened arteriole walls and capillary closure leads to – retinopathy, neuropathy, nephropathy
**Normal arteriole**

- Thin wall & wide lumen

Microscopic photograph of a cross section of a normal arteriole next to a glomerulus. The lumen is wide open to allow normal flow of blood.

**Diabetic arteriole**

- Thick wall & narrow lumen

Microscopic photograph of a cross section of an arteriole with diabetic arteriolar sclerosis. The lumen is narrowed by the thick wall thus reducing flow of blood.

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**Normal retina**

- Macula
- Optic disk

**Retinopathy**

- Hemorrhage
- Aneurysms
Microvascular disease, diabetic ulcers and gangrene
Obesity is defined by the “Body Mass Index”

Body Mass Index (BMI) = \frac{\text{Body Weight (kg)}}{\text{(Height)}^2 \text{ (m)}}
Figure 4. Relationship of body mass index to disease risks.

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Morbidly Obese
Relationship Between Weight Gain in Adulthood and Risk of Type 2 Diabetes Mellitus

The Epidemic

Changes in human behaviour over the last few decades are resulting in a dramatic increase in incidence of obesity and type 2 diabetes mellitus.
Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 years or older

**Obesity (BMI ≥30 kg/m²)**

- **1994**
- **2000**
- **2010**

- No Data
- <14.0%
- 14.0%–17.9%
- 18.0%–21.9%
- 22.0%–25.9%
- ≥26.0%

**Diabetes**

- **1994**
- **2000**
- **2010**

- No Data
- <4.5%
- 4.5%–5.9%
- 6.0%–7.4%
- 7.5%–8.9%
- ≥9.0%

Few countries have a diabetes prevalence less than 4%. The International Diabetes Federation estimates that by 2030 the global prevalence of diabetes will be 7.8%, with 438 million suffering from the disease. Another 8.4% (472 million) will have impaired glucose tolerance (a precursor of type 2 diabetes).
The human species evolved with a **thrifty genotype** - the ability to store energy producing substrates in “times of plenty” that could be used “when food was scarce”.

But now food is always abundant and we are victims of our own evolution storing calories that we do not need and becoming obese.

Certain individuals may have a genetic make up that makes them eat more and store more fat.

This kind of genetic susceptibility coupled to a modern lifestyle with less exercise and an abundance of high calorific food, has lead to the epidemic in obesity and Type 2 Diabetes.
Gene = DNA (Genome)

m RNA

Protein eg receptor (Proteome)

Function in cell eg Insulin signalling (Phenotype)

**Genetic differences**

There may be slight differences in genes between individuals (Single nucleotide polymorphisms).

This might mean that the protein produced may be very slightly different between individuals. (This explains eye colour, blood group, body shape etc)

This also applies to proteins in the cell.

For example: You might mean have protein receptors that are very slightly better at responding to insulin than I have.
It’s not fair!
Why the difference?
Genetic?
Environmental?
Both!!!
How have the genes responsible for predisposition to diabetes been identified?

1. Genetic Animal models of obesity and diabetes:

The ob⁻/ob⁻ mouse is deficient in leptin, a hormone released by adipose tissue that binds receptors in the hypothalamus and reduces appetite. The ob⁻/ob⁻ mouse overeats and becomes obese and develops type 2 DM.
Examine the human genome in patients with diabetes to see if a particular gene is always defective – linkage analysis in families, association studies in patient cohorts.
The CTLA4 gene produces a protein that inhibits the T-lymphocytes (white blood cells) that cause autoimmune destruction of the beta cells that secrete insulin. Thus polymorphisms in the CTLA4 gene could predispose to type 1 diabetes. Linkage and association analysis of chromosome suggest this.

**Linkage analysis** shows that all of the members of this family that have type 1 diabetes have inherited the G polymorphism (mutation).

**Association** shows that a significant number (20%) of type 1 diabetic patients have the G polymorphism (mutation).

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Ethnic minorities have thrifty genes that predispose to obesity and diabetes.
Prevalence of Diagnosed Diabetes by Ethnicity in UK (1999)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>% Men</th>
<th>% Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Black</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Chinese</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Indian</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Pakistani</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Bangladeshi</td>
<td>19</td>
<td>14</td>
</tr>
</tbody>
</table>

US Diabetes Prevalence by Ethnic Group

Men and Women, Age 45-74 Years

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>% with diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>10</td>
</tr>
<tr>
<td>Cuban American</td>
<td>15</td>
</tr>
<tr>
<td>Japanese American</td>
<td>20</td>
</tr>
<tr>
<td>African American</td>
<td>25</td>
</tr>
<tr>
<td>Mexican American</td>
<td>30</td>
</tr>
<tr>
<td>Puerto Rican</td>
<td>35</td>
</tr>
<tr>
<td>Pima</td>
<td>50</td>
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</table>
The increase in childhood obesity has revealed some children with genetic differences that make them develop type 2 diabetes at a young age. MODY = Maturity Onset Diabetes in the Young.
INCREASING NUMBER OF OVERWEIGHT CHILDREN AROUND THE WORLD

Percentage overweight

SOURCE: Government Office for Science
Diabetes genes code for proteins that influence either 

**insulin secretion**

or

**insulin sensitivity**

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Function</th>
<th>Effect</th>
<th>Linked to</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF-4-α, HNF-1-β, IPF-1, NeuroD1</td>
<td>Transcription factors</td>
<td>↓ Insulin secretion</td>
<td>MODY (human)</td>
</tr>
<tr>
<td>HNF-1-α</td>
<td>Transcription factor</td>
<td>↓ Insulin secretion</td>
<td>MODY</td>
</tr>
<tr>
<td>Glucokinase</td>
<td>Glucose metabolism</td>
<td>↓ Insulin secretion</td>
<td>Oji-Cree diabetes</td>
</tr>
<tr>
<td>Calpain-10</td>
<td>Protease</td>
<td>Unknown</td>
<td>Diabetes 2 in Mexican and African Americans</td>
</tr>
<tr>
<td>PPAR-γ</td>
<td>Transcription factor</td>
<td>↓ Insulin sensitivity</td>
<td>Diabetes 2</td>
</tr>
<tr>
<td>Insulin receptor</td>
<td>Transmits insulin signals into cell</td>
<td>↓ Insulin sensitivity and secretion</td>
<td>Human diabetes (rare); mouse models</td>
</tr>
<tr>
<td>IRS1 and -2</td>
<td>Insulin signaling</td>
<td>↓ Insulin sensitivity</td>
<td>Mouse models</td>
</tr>
<tr>
<td>Akt2</td>
<td>Insulin signaling</td>
<td>↓ Insulin sensitivity</td>
<td>Mouse models</td>
</tr>
<tr>
<td>11-β-HSD</td>
<td>Glucocorticoid synthesis</td>
<td>↑ Blood lipids, ↓ insulin sensitivity</td>
<td>Mouse models</td>
</tr>
<tr>
<td>UCP2</td>
<td>↓ ATP synthesis</td>
<td>↓ Insulin secretion</td>
<td>Mouse models</td>
</tr>
<tr>
<td>Resistin</td>
<td>Fat cell “hormone”</td>
<td>↓ Insulin sensitivity</td>
<td>Mouse studies</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Fat cell “hormone”</td>
<td>↑ Insulin sensitivity</td>
<td>Mouse, human studies</td>
</tr>
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**Insulin Secretion**

Glucose enters the β-cell via the GLUT 2 transporter. Glucokinase phosphorylates glucose to glucose-6-phosphate and commits it to metabolism. ATP is produced which closes ATP-sensitive K+ channels provoking membrane depolarisation that opens voltage-dependent Ca2+ channels. The Ca2+ influx releases intracellular stores of insulin by exocytosis.

Insulin binds to insulin receptors on the β-cell and stimulates transcription of the insulin gene and genes encoding proteins involved in glucose metabolism. Transcription factors implicated in this control include HNF-1, IPF-1 and NeuroD1.
GLUCOSE

GLUT4

PI3K pathway

Insulin Receptor

α α β

Insulin

PTEN

PI3,4,5 P3

PDK1

PDK2

PI3K

p110

p85

PI4,5 P2

Insulin receptor substrate

β tyrosine

Glucose transport

PKB (Akt)

GSK-3

Glycogen synthesis

mTOR (FRAP)

p70S6K

Protein synthesis
The causes of obesity: 30% of obesity is genetic but there is a large input from environment eg. diet.
Obesity is really all about calorie intake!!!
Why does **obesity** result in **type 2 diabetes**?

Waist circumference is a marker for adiposity (number and size of fat-storing cells called adipocytes).

Abdominal fat is associated with high blood levels of fatty acids and these cause insulin resistance and type 2 diabetes.

The adipocytes here are large and very metabolically active and release a lot of free fatty acids into the blood.
Adipose tissue

Fat stores → Plasma free fatty acids

Toxic to insulin secretory cells of pancreas and therefore decrease insulin secretion

Type 2 diabetes

Inhibit the insulin signalling pathway in tissues such as muscle and therefore produce insulin resistance in muscle
Insulin resistance

Glucose transport

PKB (Akt)

GSK-3

Glycogen synthesis

mTOR (FRAP)

p70S6K

Protein synthesis

Ribosomal p70S6kinase (S6K1)
cJunNH₂term kinase (JNK)
Protein Kinase C (PKCθ)

activate

FREE FATTY ACIDS
Sodium Glucose Transporter Inhibitors in Kidney increase glucose excretion in urine

Gastric Banding (Bariatric surgery)

Orlistat
Leptin analogues
Ghrelin antagonists and PYY agonists (appetite suppressants)

Thiazolidinediones
Causes uptake of fatty acids from blood into adipose tissue thus reducing insulin resistance

Sulphonylureas
Meglitinides
Incretins

Stimulate insulin secretion from the Islets of Langerhans in Pancreas

Metformin
Mimics the effect of contraction in muscle to increase glucose uptake.
Also oxidizes fatty acids thus reducing insulin resistance

Type II Diabetes
Obesity

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Sodium Glucose Transporter Inhibitors in Kidney increase glucose excretion in urine

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Orlistat
Leptin analogues
Ghrelin antagonists and PYY agonists (appetite suppressants)
Orlistat Prevents Fat Digestion and Absorption by Binding to Gastrointestinal Lipases

TG = triglyceride, MG = monoglyceride, FA = fatty acid.
This cure works!

GASTRIC BYPASS

Double row of staples creates a small pouch

This end connects to the small intestine

This end is sewn shut
Can we reduce appetite and prevent obesity?

**LEPTIN** is produced by adipose tissue to signal that fat stores are full. Signals brain to stop eating.

**GHRELIN** is produced by an empty stomach. Signals brain to start eating.

**PYY** is produced by stomach when full. Signals brain to stop eating.
There are genetic models of obesity – the ob/ob mouse is homozygous for a mutation in the leptin gene. The fa/fa rat has a mutation in the gene for the leptin receptor.

Leptin deficiency in humans is in fact rare.

Only 2 known UK cases.

Leptin administration reverses the obesity.

Human obesity actually correlates with leptin resistance – comparable to type 2 diabetes insulin resistance.
tranzyme pharma is developing TZP-301, a ghrelin antagonist for the treatment of obesity and metabolic syndrome.

has developed metreleptin – a leptin analogue and agonist that is an appetite suppressant.
Ronald MacDonald arrested in foiled terrorist plot to spread disease in Britain