Insulin induced weight gain - potential mechanisms and consequences?

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University of Oslo
Weight gain

Hyper-insulinaemia

Insulin resistance

Polonsky et al. JCI 1988;81: 442
Carbohydrates

Glucose

ENZYMES

Insulin

(I)

Reduced \( \beta \)-cell function

Glucose over-production

Liver

Pancreas

Muscle

Adipose Tissue

Increased secretion of NEFA

Reduced glucose uptake

Insulin resistance

Patophysiology of hyperglycaemia in type 2 diabetes
Insulin resistance and reduced insulin secretion in T2DM

![Graph showing changes in glucose levels and relative function over years with diabetes.]

- **Glucose**
  - Postprandial glucose
  - Fasting glucose

- **Relative function**
  - Insulin resistance
  - Beta cell failure
  - Insulin level

**Years with diabetes**

- 0
- 5
- 10
- 15
- 20
- 25
- 30
Treatment of type 2 diabetes:
A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes

**Tier 1: Well-validated core therapies**

**At diagnosis:**
Lifestyle + Metformin

**STEP 1**

- Lifestyle + Metformin + Basal insulin

**STEP 2**

- Lifestyle + Metformin + Sulfonlurea

**STEP 3**

- Lifestyle + Metformin + Intensive insulin

**Tier 2: Less well-validated therapies**

- Lifestyle + Metformin + Pioglitazone
  - No hypoglycemia
  - Oedema/CHF
  - Bone loss

- Lifestyle + Metformin + GLP-1 agonist
  - No hypoglycemia
  - Weight loss
  - Nausea/vomiting

- Lifestyle + Metformin + Sulfonlurea

- Lifestyle + Metformin + Basal insulin
A long-term, randomized, comparative study of insulin versus sulfonylurea therapy in type 2 diabetes

K.I. BIRKELAND, K.F. HANSSEN*, P. URDAL†, K. BERG‡ & S. VAALER*
From the Hormone Laboratory and *Medical Department, Aker Diabetes Research Centre, Aker Hospital, the †Department of Clinical Chemistry, Ullevål Hospital, and the ‡Institute for Medical Genetics, University of Oslo, Oslo, Norway
UKPDS*: Treatment Policies

Main Randomisation
n=4209 (82%)

342 allocated to metformin

3867

Conventional Policy
30% (n=1138)

Intensive Policy
70% (n=2729)

Sulphonylurea
n=1573

Insulin
n=1156

*United Kingdom Prospective Diabetes Study
UKPDS: Change in Weight

overweight patients

cohort, mean values

- Conventional
- Insulin
- Chlorpropamide
- Glibenclamide
- Metformin

weight change (kg)

Years from randomisation
Major weight gain (> 5 kg) in subjects with T1DM in the DCCT

- conventional treatment
- intensive insulin treatment
Articles

Causes of weight gain during insulin therapy with and without metformin in patients with Type II diabetes mellitus

S. Mäkimattila\textsuperscript{1}, K. Nikkilä\textsuperscript{2}, H. Yki-Järvinen\textsuperscript{1}

\begin{itemize}
\item Change in body weight
\item Change in dietary intake
\item FP-glucose
\item BMR
\item Change (MJ/day)
\item Δ Glucosuria
\item Δ BMR glucose – Predicted
\item Δ BMR – Observed
\item Δ BMR weight – Predicted
\item Δ Energy intake
\end{itemize}
Articles

Causes of weight gain during insulin therapy with and without metformin in patients with Type II diabetes mellitus

S. Mäkimattila¹, K. Nikkilä², H. Yki-Järvinen¹
Causes of weight gain during (intensive) insulin therapy

- Reduction in glucose (= energy) loss in the urine
- Anabolic effects of insulin
- Insulin-induced hypoglycaemia $\rightarrow$ frequent snacking
  $\rightarrow$ increased energy intake $\rightarrow$ weight gain
- Others?
Insulin treatment (NPH x 2) of T2DM for 12 months: BMI and s-leptin before and after

Aas A-M, Birkeland JCEM in press
Insulin treatment of T2DM

Changes in body weight and s-leptin

Aas A-M, Birkeland et al. Diabetologia 2006; 49: 872
Insulin treatment in patients with type 2-diabetes:
Relationship between s-leptin response to short time insulin infusion
and weight gain during insulin therapy

Hyperinsulnaemic clamp

Changes in leptin during clamp vs weight-changes 0-12 months

Aas A-M, Birkeland et al JCEM in press
Insulin treatment in patients with type 2-diabetes:

Relationship between s-leptin and BMI before and 12 mo after insulin treatment vs continuing on tablets

Insulin treatment:
Before (open, hatched) vs after 12 months (filled, solid)

Oral treatment:
Before (open, hatched) vs after 12 months (filled, solid)

Aas A-M, Birkeland et al JCEM in press
Does leptin play a role in the development of common obesity in humans?

a) Absent leptin?
b) Regulatory disorder?
c) Leptin resistance?

(Friedman & Halaas, Nature 1998)
Diabetes late complications
T2DM: Relative risk reduction* with intensive glucose lowering therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Yr</th>
<th>N</th>
<th>MI</th>
<th>CV comp</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>10</td>
<td>3867</td>
<td>16 (0.29)</td>
<td>N/A</td>
<td>6 (-10.20)</td>
</tr>
<tr>
<td>UKPDS-met.</td>
<td>10.7</td>
<td>763</td>
<td>39 (11.59)</td>
<td>N/A</td>
<td>36 (9.55)</td>
</tr>
<tr>
<td>ACCORD</td>
<td>3.5</td>
<td>10251</td>
<td>24 (8.38)</td>
<td>10 (-4.22)</td>
<td>-22 (-46.1)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5</td>
<td>11140</td>
<td>2 (-23.22)</td>
<td>6 (-6.16)</td>
<td>7 (-6.17)</td>
</tr>
<tr>
<td>VADT</td>
<td>6.3</td>
<td>1791</td>
<td>1.8 (-14.41)</td>
<td>12 (-5.26)</td>
<td>-7 (-42.19)</td>
</tr>
</tbody>
</table>

* Mean and 95% CI
**10-yrs of intensive vs conventional treatment of type 2 diabetes (UKPDS)**

<table>
<thead>
<tr>
<th>Complication</th>
<th>SU/Insulin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes complication:</td>
<td>- 12% (p=0.03)</td>
<td>- 32% (p=0.0023)</td>
</tr>
<tr>
<td>Diabetes related death:</td>
<td>n.s.</td>
<td>- 42% (p=0.017)</td>
</tr>
<tr>
<td>Total mortality:</td>
<td>n.s.</td>
<td>- 36% (p=0.011)</td>
</tr>
<tr>
<td>MI:</td>
<td>- 14% (p=0.05)</td>
<td>- 39% (p=0.01)</td>
</tr>
</tbody>
</table>
Effects of an intensified lifestyle program (ILP) vs insulin treatment (IT) in T2DM

Aas AM et al Diabetologia 2006;46:872-80
1253 participants in DIGAMI-2

Excluded 388 participants
Died/ changed treatment/ lack of information

865 participants same treatment 0 and 12 months

Group I
No pharmacological treatment (n=99)

Group II
Oral Hypoglycaemic Agents (n=250)

Group III
Insulin treatment (n=245)

Group IV
Insulin, previous and present (n=271)

Aas AM et al Diabetes Obes Metab 2009;11:323-9
<table>
<thead>
<tr>
<th></th>
<th>Group I No OHA or insulin n=99</th>
<th>Group II OHA n=250</th>
<th>Group III Insulin n=245</th>
<th>Group IV Continued insulin n=271</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [years]</strong></td>
<td>67.4 (65.2-70.0)</td>
<td>66.4 (65.2-67.7)</td>
<td>65.0 (63.6-66.3)</td>
<td>67.0 (65.7-68.3)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Male gender [n (%)]</strong></td>
<td>74 (74.7)</td>
<td>178 (71.2)</td>
<td>170 (69.4)</td>
<td>181 (66.8)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>BMI [kg/m²]</strong></td>
<td>27.1 (26.3-28.0)</td>
<td>29.0 (28.4-29.5)</td>
<td>28.7 (28.1-29.4)</td>
<td>28.9 (28.3-29.4)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Diabetes duration [years]</strong></td>
<td>1.1 (0.6-1.6)</td>
<td>5.8 (5.0-6.6)</td>
<td>6.2 (5.4-7.0)</td>
<td>13.3 (12.2-14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Previous cardiovascular disease [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>22 (22.2)</td>
<td>60 (24.0)</td>
<td>68 (27.8)</td>
<td>113 (41.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina</td>
<td>29 (29.3)</td>
<td>106 (42.4)</td>
<td>95 (38.8)</td>
<td>141 (52.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (34.3)</td>
<td>101 (40.6)</td>
<td>120 (49.0)</td>
<td>155 (57.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6 (6.1)</td>
<td>21 (8.4)</td>
<td>28 (11.4)</td>
<td>68 (25.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Bypass surgery [n (%)]</strong></td>
<td>5 (5.1)</td>
<td>20 (8.0)</td>
<td>18 (7.3)</td>
<td>58 (21.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percutaneous coronary intervention [n (%)]</td>
<td>4 (4.0)</td>
<td>21 (8.4)</td>
<td>18 (7.3)</td>
<td>33 (12.2)</td>
<td>0.062</td>
</tr>
<tr>
<td><strong>Cardiovascular disease score</strong></td>
<td>0.7 (0.5-0.9)</td>
<td>0.9 (0.8-1.1)</td>
<td>0.9 (0.8-1.1)</td>
<td>1.6 (1.4-1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Current smoker [n (%)]</strong></td>
<td>28 (28.3)</td>
<td>73 (29.3)</td>
<td>69 (28.3)</td>
<td>51 (19.0)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>HbA1c [%]</strong></td>
<td>7.0 (6.6-7.3)</td>
<td>7.2 (7.0-7.5)</td>
<td>7.3 (7.0-7.5)</td>
<td>7.4 (7.2-7.6)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>b-glucose at randomization [mmol/l]</strong></td>
<td>11.9 (11.2-12.6)</td>
<td>12.2 (11.7-12.7)</td>
<td>13.2 (12.6-13.7)</td>
<td>12.4 (11.9-12.9)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Lipids at randomization [mmol/l]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s-cholesterol</td>
<td>5.6 (5.3-5.9)</td>
<td>5.2 (5.0-5.3)</td>
<td>5.3 (5.2-5.5)</td>
<td>4.9 (4.7-5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>s-triglycerides</td>
<td>2.1 (1.7-2.5)</td>
<td>2.4 (2.1-2.7)</td>
<td>2.3 (2.1-2.6)</td>
<td>2.1 (1.9-2.4)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Mean arterial pressure [mmHg]</strong></td>
<td>95 (91-98)</td>
<td>98 (96-100)</td>
<td>98 (95-100)</td>
<td>96 (94-98)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Aas AM et al Diabetes Obes Metab 2009;11:323-9
Changes in HbA1c during the first year of the study

Error Bars show 95,0% CI of Mean
Bars show Means

Actual diabetes treatment at baseline, 3 and 12 months

Aas AM et al Diabetes Obes Metab 2009;11:323-9
Changes in body weight from baseline to 3 years

- New insulin
- Continued insulin
- OHA
- No glucose-lowering drug

n = 865 768 784 809 636 534 401 327

Aas AM et al Diabetes Obes Metab 2009;11:323-9
DIGAMI-2: CV-deaths and re-infarction according to treatment groups and weight changes during the study

Aas AM et al Diabetes Obes Metab 2009;11:323-9
Insulin-induced weight gain - Conclusions

- Insulin therapy is life-saving in T1DM and beneficial in T2DM if it lowers blood glucose

However

- It may result in weight gain, due to
  - Reduced glucose loss in the urine
  - Possible increase in hypos and snacking
  - Anabolic effect of insulin
  - Stimulation of leptin secretion and leptin resistance?
- It may have adverse effects on CV risk?
  - Through weight-related effects on
    - Inflammation
    - Lipids
    - BP