Do we need alternative routes of insulin administration (inhaled insulin) in Type 2 diabetes?

Cons: Suad Efendic
Karolinska Institutet, Sweden
The Diabetes Management Situation Today

- Diabetes is a growing global epidemic
- Lack of glycemic control leads to complications and high associated healthcare costs
- Despite clear guidelines, current glycemic control rates are poor and are getting even worse
- Insulin is often used as the treatment of last resort
- Physicians treating diabetes, and patients with the disease, are looking for better solutions
Majority of Type 2 Diabetes Patients in EU Have Inadequate Glycemic Control


Percentage of subjects

<table>
<thead>
<tr>
<th>HbA$\text{\textsubscript{1c}}$ (%)</th>
<th>≤ 6.5%</th>
<th>&gt; 6.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>31%</td>
<td>69%</td>
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</table>

The Bottom Line

- Normalization of blood glucose is crucial for prevention and treatment of vascular complications
# Glycemic Targets

<table>
<thead>
<tr>
<th></th>
<th>ADA</th>
<th>AACE</th>
<th>IDF (Europe)</th>
</tr>
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<tbody>
<tr>
<td>HbA$_1c$ (%)</td>
<td>&lt; 7</td>
<td>≤ 6.5</td>
<td>≤ 6.5</td>
</tr>
</tbody>
</table>

Diabetes market and disease overview (8)

Source: NDR annual report 2005
Initiating insulin therapy in type 2 diabetes

The main options for introduction of insulin treatment include intermediate- or long-acting basal insulin or biphasic insulin formulations containing both basal and rapid-acting components.

The combinations treatment, based on one or two insulin injections daily plus oral therapy is usually more effective than insulin monotherapy.
During last years are published studies comparing treatment with intermediate acting NPH insulin and long-acting insulin glargine.

The average glycemic control improved similarly with both insulins. The proportion of patients achieving target HbA1C (≤ 7.0%) was about 30% but overall symptomatic and nocturnal hyperglycemia was less in insulin glargine group compared with NPH arm.

The risk for severe hypoglycemia and severe nocturnal hypoglycemia were reduced with insulin glargine by 48% and 59%, respectively.
Initiating insulin therapy in type 2 diabetes

In the treat to target trial overweight patients with inadequate glycemic control were randomized to 24 week treatment with bedtime glargine or NPH.

The dose of insulin was titrated using a simple algorithm to achieve a target fasting plasma glucose of 5.5 mmol/l.

Mean HbA1C values at the end point were almost identical with two therapies. 60% of patients attained HbA1C ≤ 7.0%. However 25% more patients on glargine attained this HbA1C level without documented nocturnal hypoglycemia (≤ 4.0 mmol/l).
Postprandial blood glucose levels play the most important role in regulation of overall glycemic control.

They must be nearly normalized to get HbA1C values near targets proposed by ADA (<7%) or AACE and IDF (≤ 6.5%).

To meet this expectation the fast-acting insulin component is added to basal insulin. The biphasic insulin aspart 70/30 (BIAsp 70/30) is an insulin analog containing 30% soluble insulin aspart and 70% insulin aspart crystallized with protamine.

This insulin is marketed as Novolog Mix 70/30 in USA and Novo Mix 30 elsewhere.
Attainment of glycemic goals in type 2 diabetes with biphasic insulin aspart 70/30

In patients with type 2 diabetes and failing oral agent therapy, Garber et al investigated efficacy of BIAsp 70/30 treatment given once-, twice- or thrice daily.

Importantly with three daily insulin injections of BIAsp 70/30 as many as 60% of patients reached HbA1C levels ≤ 6.5 whereas 77% achieved HbA1C <7%.
The optimal insulin treatment in patients with type 2 diabetes

1. Biphasic insulin aspart 70/30.
2. Glargine with a low fasting plasma glucose as target (5.5 mmol/l).
3. Levemir?
Problem when treating patients with type 2 diabetes:

- Complexity of the pathogenesis!
Normalise hormonal responses

- insulin
- glucagon

Normalise insulin sensitivity

- somatostatin

(and/or prolong transit time for nutrients in G-I tract)
Glucagon like polypeptide – 1
(GLP – 1)
Gutniak M. Orskov C, Holst JJ, Ahren B, Efendic S

Antidiabetogenic effect of glucagon like peptide-1 (7-36) amide in normal subjects and patients with diabetes mellitus

Summary

The antidiabetogenic effect of GLP-1 could be accounted for by following effects:
- stimulation of insulin secretion
- inhibition of glucagon release
- delay of gastric emptying
- increase of insulin sensitivity
Additional islet effects of GLP-1

- Stimulates insulin gene expression
- Stimulates insulin biosynthesis
- Stimulates β-cell proliferation and survival
- Stimulates differentiation of exocrine cells or islet precursors toward β-cell phenotype
If these interesting findings can be replicated, they may lead to new insights into factors governing insulin sensitivity, and GLP-1 analogues may become useful in the treatment of patients with type 2 diabetes.
**GLP-1 analogs**
Exenatide (exendin -4) (Eli Lilly)
Liraglutide (NN2211) (Novo Nordisk)

**DPP IV inhibitors**
CLAF 2303 (Novartis)
MK-0431 (Merck & Co, Ivc)
Development of Exenatide: An Incretin Mimetic

Exenatide (Exendin-4)
- Synthetic version of salivary protein found in the Gila monster
- Approximately 50% identity with human GLP-1
  - Binds to known human GLP-1 receptors on β cells \textit{in vitro}
  - Resistant to DPP-IV inactivation

Efficacy of Exenatide Compared with Twice-Daily Biphasic Insulin Aspart 30/70 in Patients with Type 2 Diabetes Using a Sulphonylurea and Metformin

Michael A. Nauck¹; Santiago Duran²; Dennis Kim³; Don Johns⁴; Andreas Festa⁵; Michael Trautmann⁶

Bad Lauterberg, Germany ¹; Seville, Spain ²; San Diego, United States ³; Indianapolis, United States ⁴; Vienna, Austria ⁵; Hamburg, Germany ⁶
## Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Exenatide</th>
<th>Premixed Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.8 (8.7)</td>
<td>58.5 (9.2)</td>
</tr>
<tr>
<td>Gender, male %</td>
<td>53.4</td>
<td>49.2</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>85.7 (15.7)</td>
<td>83.4 (15.6)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.6 (4.0)</td>
<td>30.2 (4.2)</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>11.0 (2.7)</td>
<td>11.3 (2.8)</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>8.6 (1.0)</td>
<td>8.6 (1.1)</td>
</tr>
<tr>
<td>Duration of diabetes, y</td>
<td>9.8 (6.3)</td>
<td>10.0 (6.2)</td>
</tr>
</tbody>
</table>

ITT sample, mean (SD) shown
Time Course of HbA$_{1c}$

Per protocol sample, mean (SE) shown; difference in HbA1c change at endpoint was -0.15%, -0.32 to 0.01%; $p=.074$ (exenatide minus insulin [95% CI, p-value])
Time Course of Change in Body Weight

Exenatide vs Premixed Insulin at postbaseline time points

ITT sample, mean (SE) shown
*p<.001, Exenatide vs premixed insulin at postbaseline time points

Weeks

Change in Body Weight (kg)

+ 2.9 kg
- 2.5 kg
5.4 kg

0 2 4 8 12 16 28 40 52
Is there advantage of using inhaled insulin (Exubera) in patients with type 2 diabetes and accepting insulin treatment?

NO?
Why No?

1. Expensive.
2. Continuous monitoring of lung function.
3. Probably less efficacy than the above discussed insulin regimes with a low blood glucose as a target.
4. Increased antibodies.
Ex-manufacturer Price (WAC is used for US, net prices ex-US)

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<thead>
<tr>
<th></th>
<th>UK</th>
<th>Germany</th>
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<tbody>
<tr>
<td></td>
<td>US $ (Obs!)</td>
<td>Daily dose based on WHO DDD (daily dose defined)</td>
</tr>
<tr>
<td>Exubera</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>13 mg</td>
<td>13 mg</td>
</tr>
<tr>
<td>Humulin N (pre-loaded Syringe/Pen Insulin)</td>
<td>1,13</td>
<td>1,06</td>
</tr>
<tr>
<td>Humalog (pre-loaded Syringe/Pen Insulin)</td>
<td>1,23 40 IU</td>
<td>1,45 40 IU</td>
</tr>
<tr>
<td>Lantus (pre-loaded Syringe/Pen Insulin)</td>
<td>1,64 40 IU</td>
<td>1,78 40 IU</td>
</tr>
<tr>
<td>Avandia</td>
<td>2,07 8 mg</td>
<td>2,31 8 mg</td>
</tr>
<tr>
<td>Actos</td>
<td>1,87 30 mg</td>
<td>2,32 30 mg</td>
</tr>
</tbody>
</table>
What is place of inhaled insulin in the modern treatment of patients with type 2 diabetes?

To facilitate acceptance of insulin treatment.

To decrease the time between the secondary failure to oral treatment and initiation of insulin treatment.
Policy in Sweden

Exubera is subsidized for the treatment of adult patients who exhibit a poor glycemic control due to documented difficulties to inject insulin:

1. Adult patients with type 2 diabetes treated with at least two oral antidiabetic drugs

2. Adult patients with type 1 diabetes, in combination with medium- or long-lasting insulin given subcutaneously, provided that benefits of using inhaled insulin prevail over risks
What is place of inhaled insulin in the modern treatment of patients with type 2 diabetes?

In this context is of special interest study of Freemantle et al which included 779 patients from seven countries and with type 2 diabetes and HbA1C > 8%. The current therapy included dietary measures and/or antidiabetic agents (OAD).

Patients were randomized to receive either information about the risks and benefits of all current licensed treatment options only (OAD’s and/or subcutaneous insulin) or information about potential risks or benefits of licensed treatment and inhaled insulin.

In the group offered inhaled insulin as an option 43.2% of patients opted for treatment that included insulin as compared with 15.5% of patients who were offered standard therapies only.
Conclusions

1. Long-acting GLP-1 analogs may substitute for insulin treatment in a majority of patients with type 2 diabetes exhibiting failure to oral treatment

2. Biphasic insulin aspart 70/30, glargine and levemir constitute the optimal insulin treatment in patients with type 2 diabetes

3. Exubera is recommended to adult patients with poor glycemic control due to documented difficulties to inject insulin