Abstract

Type 2 diabetes is a progressive disease in which insulin secretion diminishes continuously in time. There is a strong correlation between glycaemic burden and late complications in type 1 and type 2 diabetes. In order to avoid these complications, ADA currently recommends HbA1c levels of < 7.0% and the IDF and AACE recommend a target of ≤ 6.5%. Glycaemic control can be achieved initially by diet and exercise habits and/or the prescription of ≥1 OAD. Exogenous insulin therapy is required in addition to or as an alternative to OAD therapy as type 2 diabetes progresses. Insulin therapy is often delayed due to concerns about injection, hypoglycaemia, and weight gain. Insulin analogues, due to their properties, may improve patient adherence to initiating insulin therapy in an earlier stage of the disease.

Novo Nordisk initiated and conducted in May 2007 the 'HbA1c' Project in 13 diabetes centres in Romania. The HbA1c measurements in 9,000 type 2 diabetic patients diagnosed for 6-8 years on OADs and/or human insulin treatment showed that only 19% were < 7% and 81% were ≥ 7%.

Key words: type 2 diabetes, diabetes complications, HbA1c, insulin initiation

Type 2 diabetes is a progressive disease in which insulin secretion, particularly in response to prandial stimuli, diminishes in the setting of insulin resistance. Metabolic control deteriorates relentlessly as the duration of diabetes increases and beta-cell function is progressively lost.

Glucolipotoxicity has a very important role in this process (fig. 1).

Findings from the U.K. Prospective Diabetes Study (UKPDS) showed that deterioration in beta-cell function occurred in the diet-only treatment group as well as in patients treated with sulfonylureas or metformin, suggesting that neither of these agents slowed the rate of decline.

Also, outcomes from the U.K. Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) demonstrate a strong correlation between glycaemic burden and microvascular complications in both type 1 and type 2 diabetes. According to the Kumamoto Study, HbA1c < 6.5%, fasting blood glucose...
concentration <110 mg/dl, and 2-h postprandial blood glucose concentration <180 mg/dl constitute the glycaemic threshold to prevent the onset and progression of diabetic microvascular complications in type 2 diabetes.

**Type 2 diabetes is progressive: Beta-cell dysfunction declines with time**

![Graph showing the decline of beta-cell function with time from diagnosis, based on data from UKPDS 24, 1998](image)

Almost 80% of patients treated with sulphonylureas require insulin by 9 years post-diagnosis.

**Fig. 1**

**Table 1**

**ADA and AACE glycaemic targets**

<table>
<thead>
<tr>
<th></th>
<th>ADA</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>&lt; 7</td>
<td>≤ 6.5</td>
</tr>
<tr>
<td>Fasting/ preprandial* (mg/dl)</td>
<td>90–130</td>
<td>&lt; 110</td>
</tr>
<tr>
<td>2-hour postprandial (mg/dl)</td>
<td>&lt; 180†</td>
<td>&lt; 140</td>
</tr>
</tbody>
</table>

*Plasma equivalent.
†Peak postprandial (~1 hour).

A stricter glycaemic control is necessary to prevent the macrovascular complications of diabetes.

Early glycaemic control is vital because of “glycaemic memory”, as was shown in the EDIC (Epidemiology of Diabetes Interventions and Complications) Study. Four years after the end of the DCCT trial, despite increasing hyperglycaemia, the reduction in the risk of progressive retinopathy and nephropathy persisted in the intensive therapy...
The American Diabetes Association currently recommends HbA1c levels of < 7.0% based on evidence that stricter glycaemic control might be necessary to prevent macrovascular complications. The International Diabetes Federation and American Association of Clinical Endocrinologists recommend a target of ≤ 6.5% (table 1).

HbA1c levels reflect overall glycaemic exposure over the past 2–3 months and are determined by both fasting and postprandial plasma glucose. Because postprandial hyperglycaemia has been implicated as a risk factor for macrovascular complications and cardiovascular disease, AACE has recommended aggressive treatment goals for 2-h postprandial glucose (140 mg/dl or less).

The American Diabetes Association estimates that the risk of diabetes-related mortality increases 25% for each 1% increase in HbA1c. Each percentage point increase in HbA1c has also been estimated to correspond to a 35% increase in the risk of microvascular complications and an 18% increase in the risk of myocardial infarction (fatal plus non-fatal).

Glycaemic control can be achieved initially by interventions to improve diet and exercise habits and/or the prescription of ≥1 oral antidiabetic drug (OAD), such as insulin secretagogue and/or metformin.

However, in patients in whom type 2 DM progresses as a result of declining beta-cell function, exogenous insulin therapy is required in addition to or as an alternative to OAD therapy. Recent guidelines and targets for glycaemic control published by the International Diabetes Federation encourage the use of insulin at earlier stages in the disease process than has been conventional, but many patients and health care professionals delay insulin therapy due to concerns about injection-site pain, hypoglycaemia, and weight gain (fig 2 and 3).

**Patient attitudes to initiating insulin therapy: Data from the DAWN* study**

<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th>Other countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>% patients agreeing</td>
<td>53.1</td>
<td>52.6</td>
</tr>
</tbody>
</table>

Healthcare professionals’ attitudes to initiating insulin therapy: *Data from the DAWN* study

- Health care professionals are reluctant to initiate insulin
  - ‘Earlier introduction of insulin would decrease the overall cost of diabetes care in the long term’
  - ‘I prefer to delay initiation of insulin until absolutely essential’

% agreeing to statement

<table>
<thead>
<tr>
<th></th>
<th>Primary care physician</th>
<th>Specialist</th>
<th>Nurse</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Earlier introduction of insulin would decrease the overall cost of diabetes care in the long term’</td>
<td>48</td>
<td>54</td>
<td>49</td>
</tr>
<tr>
<td>‘I prefer to delay initiation of insulin until absolutely essential’</td>
<td>59</td>
<td>47</td>
<td>53</td>
</tr>
</tbody>
</table>

*Fig. 2

There is no consensus concerning the best ways to overcome these barriers when initiating insulin therapy.

The addition of a QD or BID long-acting basal insulin formulation to an existing OAD regimen, followed by aggressive titration of the dose to achieve glycaemic targets has gained popularity in recent years. Treatment intensification through the subsequent addition of a mealtime insulin injection can be undertaken at a later stage, as needed, to achieve target levels of glycaemia if treatment with basal insulin plus OAD is not sufficient.

Insulin therapy is associated with increased risk of daytime and nocturnal hypoglycaemia, which has been attributed to the pharmacodynamic properties of traditional human insulin preparations. Intermediate and long-acting human insulin preparations, such as NPH insulin, have pronounced insulin peaks 5 to 7 hours after injection, resulting in increased risk of nocturnal hypoglycaemia and duration of action that is too short to maintain glycaemic control throughout the night. Furthermore, the dosing precision with NPH insulin is often highly variable due to inadequate resuspension.

Regular human insulin injected at mealtimes has a slower onset and a more prolonged action than endogenous insulin, and consequently the combination of these human insulin results in high postprandial blood glucose excursions and risk of hypoglycaemia between meals and overnight.

Insulin analogues have been developed to enable patients with diabetes mellitus to achieve near-normal glucose levels with decreased risk of hypoglycaemia and less variability.

*Fig. 3

*Diabetes Attitudes, Wishes and Needs: A global study conducted by Novo Nordisk in collaboration with IDF and an expert advisory panel. Adapted from: Korytkowski M. Int J Obesity 2002;26(Suppl 3):S1-S7*
A major deterrent to start insulin therapy is also the risk of weight gain, which is associated with poor cardiovascular outcomes\textsuperscript{19}. Studies have shown that a 2.5\% reduction in HbA\textsubscript{1c} is associated with a 5 kg increase in weight, more commonly occurring in women than in men\textsuperscript{20}.

Insulin detemir has not been associated with a significant increase in body weight in patients with type 1 and type 2 diabetes mellitus. Significantly less weight gain was seen in patients with type 2 diabetes. These is a constant finding in all detemir interventional clinical trials and also, in the large observational study PREDICTIVE\textsuperscript{TM} \textsuperscript{21-34}

So, insulin analogues may significantly improve type 2 diabetes patient’s adherence to initiating insulin therapy in an earlier stage of the disease.

In 2002, mean HbA\textsubscript{1c} values in 8 Western European countries were above 7\%\textsuperscript{35} (fig. 4).

![Type 2 diabetic patients on diet, exercise, OAD or insulin](image)

**Fig. 4**

Mean HbA\textsubscript{1c} (%) in Europe
Adapted after Massi-Benedetti M. Diabetologia 2002;45:S1-4 (CODE-2)
HbA_1c in 3658 type 2 diabetic patients on insulin

![Graph showing HbA_1c distribution](image)

Fig. 5

Also, in 2004, combined data from IMS Disease Analyzer Germany and UK, showed that 78% of 3658 type 2 diabetic patients had mean HbA_1c values above ADA targets of <7% \(^{36,37}\) (fig. 5).

Novo Nordisk, initiated and conducted the 'HbA1c' Project in 13 diabetes centres in Romania, involving more than 200 diabetologists.

The objective of this project was to evaluate the current status of the metabolic control, determined through HbA_1c measurement in type 2 diabetes patients.

The project, which took part in May 2007 included HbA_1c measurements in 9,000 type 2 diabetic patients on OADs and/or human insulin treatment for 6-8 years.

The data from this project shows that 83% of investigated type 2 diabetic patients had HbA_1c ≥ 7% (table 2).

Table 2. Results of HbA1c measurements, May 2007

<table>
<thead>
<tr>
<th>Hb A1c</th>
<th>OAD treatment</th>
<th>HM</th>
<th>HM+ OAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb A1c &lt; 7</td>
<td>4908</td>
<td>3703</td>
<td>72</td>
</tr>
<tr>
<td>Hb A1c between 7 - 9</td>
<td>807</td>
<td>1305</td>
<td>23</td>
</tr>
<tr>
<td>Hb A1c &gt; 9</td>
<td>1456</td>
<td>2816</td>
<td>38</td>
</tr>
</tbody>
</table>

Total HbA1c > 7% | 1456 | 2816 | 61 |

OAD treatment: 1968 | 26% | 40% | 33% | 74%

HM: | 669 | 1305 | 1511 | 2816 |

HM+ OAD: 72 | 19% | 36% | 45% | 81%
In conclusion, type 2 diabetes is a progressive disease, in which the glycaemic burden is associated with the development of late complications. The development of these complications affects not only the progression and management of diabetes but also contributes to higher morbidity and mortality in patients with Type 2 diabetes. Complications have important effects on patient’s quality of life as well as socio-economic implications. The treatment strategy implies measures to achieve metabolic control and to correct associated metabolic imbalances in order to prevent/delay progression of late diabetic complications and improve the quality of life.

But, the majority of type 2 diabetic patients do not reach and/or maintain glycaemic targets. There are some approaches which allow patients’ empowerment to achieve glycaemic targets as:
- Modern insulins
- Improved insulin devices
- Simple titration guidelines for patients (home adjustments)
- Continuous Blood Glucose Monitoring (CBGM)

New and more comprehensive efforts are necessary in our country to improve the metabolic control of type 2 diabetes.

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