

## Tight glycaemic control and new modalities in the treatment of diabetes mellitus

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There has been evidence for the effect of tight glycaemic control on diabetes-related complications, in particular microvascular complications. Two large prospective studies, the Diabetes Control Complications Trial and the United Kingdom Prospective Diabetes Study, have shown in large cohorts of Type 1 and Type 2 diabetic patients the beneficial effects of tight control on microvascular complications. The development of newer agents like insulin analogues and, in the near future, inhaled insulin as well as new oral compounds groups with longer actions, meal oriented short lived effects and

insulin sensitizers will contribute to achieving better diabetic control. The new evolving treatment paradigm may well be to initiate combination therapy right from the onset of diabetes to address the pathogenetic defects and to promptly add supplemental insulin therapy if glycaemic goals are not achieved.

**Key words:** Glycaemic control, DCCT, UKPDS, insulins, oral agents

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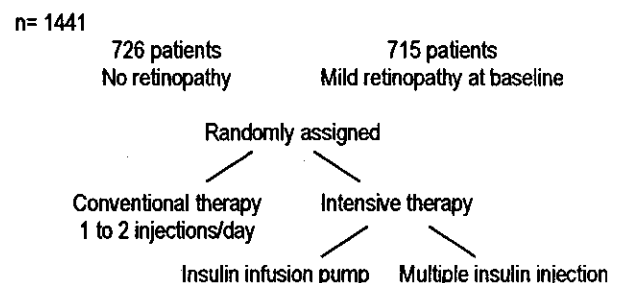
### Tight glycaemia: Is it beneficial and how is it achieved?

Over the last few years, there has been growing evidence that effective glycaemic control can ameliorate the course of microvascular lesions in patients with Type 1 and Type 2 diabetes mellitus (DM), especially with respect to retinopathy and nephropathy.

The Diabetes Control and Complications Trial (DCCT)<sup>1,2</sup> has established in 1993 that better control means fewer microvascular

complications. Premature mortality and morbidity in Type 1 DM result from cardiovascular disease, retinopathy, renal failure, and neuropathy. The DCCT, a long-term prospective randomized controlled multicenter trial, studied the course of 1441 patients with Type 1 DM, and was designed to answer two questions:

1. Whether intensive glycaemic control could prevent microvascular disease from developing;
2. Whether it could arrest or reverse early microvascular complications already present (with retinopathy and nephropathy as the primary end points).



Follow up mean 6.5 years

Study of the 1441 patients with Type 1 as regards development of progression of retinopathy showed the following:

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**Results of Intensive therapy**

Primary Intervention	Secondary Intervention
	Risk reduction
Retinopathy 76%	Progression 54%
	Proliferative retinopathy 47%

**Based on the DCCT results what should the goals of treatment be?**

Complete normalization of glycemic level if possible with 2 targets:

**Target 1**

Self monitoring of blood glucose (SMBG)

Pre meals 4.4 – 6.7 mmol/L

Bed time 5.6 – 7.8 mmol/L

**Target 2**

Glycated haemoglobin (HbA<sub>1C</sub>)

Average HbA<sub>1C</sub>

7.2% among intensively treated group

9% among conventional treated group

Normal range of HbA<sub>1C</sub> in DCCT 4-6%.

Individual treatment goals should take into account:

- the patient's capacity to understand and carry out the treatment regimen;
- the patient risk for severe hypoglycemia.

Other factors to be taken into consideration:

Very young or old age, end stage renal disease, advanced cardio vascular or cerebro vascular disease.

**Is extrapolation of the DCCT results to Type 2 DM possible?**

Yes, as far as microangiopathic complications are concerned, the pathogenesis is probably similar in all forms of diabetes. The same rules for prevention will apply but the potential risks of intensified treatment may be different in Type 2 diabetes.

**United Kingdom Prospective Diabetes Study (UKPDS)<sup>3,4,5,6,7,8,9</sup>**

This is the largest and longest multicenter, intervention prospective study of multiple therapies in Type 2 DM.

**Key aims**

- To determine whether treatment aimed at near normal plasma glucose levels, <6 mmol/l, reduces morbidity and improves life expectancy;

- To determine whether diet alone, sulphonylurea, insulin or metformin therapy has a particular advantage in terms of improving prognosis;
- To determine whether any specific therapy has deleterious major side effects;
- To determine whether any of the therapies have health care advantages, decreasing the number of days of lost normal activity or the number of hospital admissions;
- To determine whether certain clinical and laboratory measurements, including both possible risk factors and indices of early vascular disease, are useful predictors of subsequent complications.

The UKPDS study recruited a total of 5,102 Type 2 diabetic patients in 23 clinical centers in the UK. The question to answer was: "Can complications of Type 2 diabetes be prevented by improved glycemic control and improved blood pressure control?"

Secondly, the study was also aimed at assessing the safety of therapies used to treat the disease.

After recruitment, 82% of patients could be randomized to either conventional policy or intensive policy groups (in the latter, further allocating patients to sulphonylurea or insulin treatments). The median follow-up was 10 years.

Intensive treatment achieved better fasting blood glucose (1.8 mmol/l lower) and better mean HbA<sub>1C</sub> (0.9% less; mean: 7% versus 7.9%) in the conventional treated group.

Intensive policy achieved a risk reduction of diabetes related complications: 12% for any diabetic-related end-points, 16% for myocardial infarction, 25% for microvascular end-points, and 24% for cataract extraction.

For surrogate end-points there was a risk reduction of 21% for progression of retinopathy and 33% for microalbuminuria.

The epidemiological assessment of the glucose control study showed that improved glycemic control was associated with a risk reduction for diabetes-related endpoints, diabetes related deaths, all cause mortality, myocardial infarction, stroke, microvascular endpoints, and cataract extraction.

In the Blood Pressure Control study a total of 1,148 were randomized to tight or less tight blood pressure control, achieving a significant reduction of blood pressure in the former group.

Tight blood pressure control achieved a risk reduction of 25% for any diabetes-related endpoint, 32% for diabetes-related deaths, 44% for stroke, 37% for microvascular endpoints, 56% for heart failure, 34% for retinopathy progression, and 47% for deterioration of vision.

The epidemiological assessment of the Blood Pressure Control study revealed that improved blood pressure control was associated with a risk reduction for any diabetes related endpoint, diabetes related deaths, all cause mortality, myocardial infarction, stroke, microvascular endpoints, and heart failure.

Therefore as physicians planning treatment based on the above landmark studies in DM, we have to target the following tight glycemic and blood pressure control:

- FPG <6mmol/L and HbA<sub>1c</sub> 7%
- Tight Blood pressure <145 / <80 mm Hg
- Manage hyperlipidaemia
- Advice on smoking

To achieve such goals is particularly difficult in Type 2 diabetic patients.

**What are some of the newer therapeutic modalities available to help in better glycemic control?**

**New Insulin preparations—How do they work?**<sup>10,11,12,13,14</sup>

What is the treatment profile?

Insulin analogues with pharmacokinetic profiles that differ from those of existing insulin preparations have been developed for the use in insulin treated patients. The limiting step in absorption of subcutaneously administered regular insulin is the rate of dissociation of the insulin molecules from a hexamer to a dimer and monomer. Change of amino acid sequence in the region of B27 B30 of the insulin molecule leads to monomeric insulins (insulin lispro, insulin aspart), which are more rapidly absorbed

after subcutaneous injection, achieving peak plasma concentrations about twice as high and within approximately half the time compared to soluble insulin. Despite a clear reduction of postprandial glucose concentrations when monomeric insulins are used, only slight improvements of either HbA<sub>1c</sub> or frequency of hypoglycemia were observed in clinical trials.

**Insulin Aspart (Novolog; Norvo Nordisk)  
Insulin lispro (Eli Lilly)**

Insulin aspart appears similar to lispro insulin and to endogenous insulin in healthy individuals as regards its pharmacokinetics and pharmacodynamics.

Premeal insulin doses should be administered just before eating. Day time glycemic control was better with insulin aspart and lispro than with regular insulin treated diabetes but night control was poorer. No difference in blood glucose control, as assessed by serum fructosamine, was observed. Hypoglycemia was observed. Hypoglycemic episodes requiring third party intervention occurred less frequently during therapy with insulin lispro and aspart. The overall incidence of all hypoglycemic episodes was similar between the groups of patients on insulin lispro aspart and on regular insulin.

**Insulin Glargine**

Insulin glargine is a recombinant human insulin analogue that is a long acting once-daily based insulin for use in patients with Type 1 or Type 2 DM.

Principles of retardation include increasing the isoelectric point of human insulin towards a more neutral pH or binding of insulin via an acylated fatty acid. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the b-chain which is more soluble at acidic pH and less soluble at physiological pH compared with natural human insulin. Therefore, it precipitates locally in the tissue after subcutaneous injection, which delays its absorption and thereby prolongs its duration of action. The results of studies in healthy subjects and

diabetic patients have shown that insulin glargine is a long-acting insulin that mimics the normal physiological basal insulin secretion when injected once daily.

Several comparative studies were carried out to evaluate insulin glargine in comparison to NPH insulin both in Type 1 and Type 2 DM. A marked improvement in FPG was reported with a reduction in FPG value in the range 2.6 to 2.8 mmol/L in the insulin glargine group compared to 2.3 mmol/L in the NPH insulin group. There was no difference between the levels of fructosamine, HbA<sub>1C</sub> or frequency of hypoglycemia although insulin glargine may be associated with less nocturnal hypoglycemia than once-daily NPH insulin.

#### **New ways of giving insulins: the role of inhalation**

Human studies have shown that regular insulin formulations are well absorbed by the lung. The variability in the glucose response is as good as from injection. Using the inhaled insulin delivery system (INH), three studies in diabetic patients have been conducted for 3 months. A study in 70 Type 1 diabetic patients compared a pre-meal INH plus bedtime s.c. ultralente with a usual mixed s.c. regimen (two to three injections/day). Neither glycemic control nor hypoglycemia incidence and severity differed between the groups. The same results were obtained in a study similarly designed in Type 2 diabetic patients. In an additional study, INH was added to Type 2 diabetics failing oral agent therapy. After 3 months of therapy the inhaled add-on therapy showed a remarkable improvement in HbA<sub>1C</sub> of 2.4%. Despite this dramatic improvement of metabolic control only one severe hypoglycemic event was noted.

A 15-item questionnaire in the Type 1 diabetic patients also suggested a better overall patient satisfaction with INH, mainly due to items related to increased convenience and ease of use.

The general safety of INH was similar to injectable insulin in all studies. Pulmonary function tests did not change over time.

#### **Inhaled Pulmonary Delivery System**

Phase III studies of Inhaled Therapeutic Systems' Inhaled Pulmonary Delivery System (Inhaled Therapeutic Systems/Pfizer) are ongoing. The inhaler delivers a fine-powered formulation of human regular insulin into the lungs. The particles are <5 µm in diameter and dissolve in the alveoli, releasing the insulin so that it can be absorbed and transported by the pulmonary vasculature. The powder is contained in blister packs and is delivered using an inhalation device.

#### **New oral agents: How effective are they?<sup>14,15,16</sup>**

The use of oral antidiabetic drugs is the treatment domain of Type 2 diabetes. The advent of new oral agents has not changed this rule. In the post-UKPDS-era, however, lower HbA<sub>1C</sub> targets than previously thought have to be achieved, close to the normal range in younger patients, and below 8% even in the elderly. The new compounds, the recent sulphonylurea gliclazide 30mg (Diamicon MR) and glimepiride, the likewise insulin-releasing potassium-channel blocker repaglinide, the alphaglucoisidase inhibitor miglitol, and the insulin sensitizing thiazolidindiones, (rosiglitazone and pioglitazone) have a comparable blood glucose lowering potential as older anti-diabetic drugs, for which an efficacy range between 0.5 to 1.5% HbA<sub>1C</sub> lowering capacity has been established. The once-daily dosing of gliclazide 30mg and glimepiride is appropriate both for mono and combination therapy. The meal oriented short-lived effect of repaglinide allows a particularly flexible lifestyle, miglitol is targeted against postprandial hyperglycemia, and the insulin-sensitizers lead to a more prominent reduction of fasting hyperglycemia. Hence, to make an appropriate selection, quality of life parameters as well as metabolic phenotyping in terms of insulin resistance versus insulin deficiency, and postprandial versus fasting hyperglycemia need to be considered in the individual patient. As far as side effects are concerned, hypoglycemia, weight gain, gastrointestinal symptoms, kidney and liver function have to be taken into account. At that end, lower doses of any drug treatment

option will create lesser side effects, and early combination schedules seem to be preferable. All available options of drug treatment including that of the new oral agents, are suitable for combination with any of the other alternatives.

### Focus on Thiazolidinediones<sup>17,18,19</sup>

Currently available Thiazolidinediones (TZDs) are rosiglitazone and pioglitazone. They act as 'insulin sensitizers' providing a novel means to improve glycemic control by reducing insulin resistance.

A condition of insulin resistance underpins the pathogenesis of Type 2 DM. It is also fundamental to the development of a syndrome of cardiovascular risk factors that includes hyperinsulinemia, dyslipidemia, hypertension, atherosclerosis and a procoagulant state as well as visceral obesity and hyperglycemia.

The precise mechanism of action of TZDs is not completely understood. These drugs improve glycemic control by increasing insulin sensitivity. The primary mechanism of action appears to be the direct stimulation of a family of receptors on the nuclear surface of cells that are responsible for the modulation of lipid homeostasis, adipocyte differentiation, and insulin action. Thiazolidinediones are potent and highly selective agonists for one of the isoforms in this family of receptors known as peroxisome-proliferator-activated receptor-gamma (PPAR). The thiazolidinediones also display some cross reactivity to the other isoforms in the PPAR family, PPAR $\alpha$  and PPAR $\gamma$ . Different relative affinities of various TZDs for these three receptor types may explain the different effects these agents have on lipid profiles.

PPAR $\gamma$  is probably the most important of these three receptors in terms of antidiabetic action of TZDs. A relationship between ability to stimulate PPAR $\gamma$  and antihyperglycemic activity has been reported. Thiazolidinediones may cause a reduction in the number of large adipocytes and an increase in the number of small adipocytes, leading to lower free fatty acid and triglyceride levels and improved insulin sensitivity. The relative importance of

each of these mechanisms is not currently understood.

### Indications

#### Monotherapy in Type 2 DM

Oral combination with metformin (in the obese)

Oral combination with a sulphonylurea

TZDs often produce a greater glucose lowering effect when used in combination therapy suggesting an additive effect when combined with metformin or sulphonylurea.

Type 2 diabetes with inadequate glycemic control by maximally effective or maximally tolerated treatment with metformin or a sulphonylurea:

- Type of therapy - Oral combination with metformin (in the overweight) or a Sulphonylurea (if not suited to a metformin/sulphonylurea combination).
- Starting treatment - Rosiglitazone usually 4 mg/day, increased to 8 mg/day. Pioglitazone usually 15 mg/day, increased to 30 mg/day.
- Contraindications - Cardiac failure or history of cardiac failure; impaired liver function; known hypersensitivity to these agents.
- Side effects - Fluid retention, increased plasma volume, decreased hematocrit, decreased hemoglobin. Risk of edema and anemia. Weight gain and risk of hypoglycemia. Resumption of ovulation in polycystic ovaries syndrome.
- Precautions - Monitor for contraindications, notably for heart failure, anemia, edema and liver enzymes (e.g. alanine transaminase). Potential effect of pioglitazone on oral contraceptive activity.

### Key messages

- TZDs are a new class of 'insulin sensitizers'.
- TZDs are PPAR agonists.
- TZDs exert a slowly generated antihyperglycemic effect.
- TZDs are currently recommended in combination with metformin or a sulphonylurea.
- TZDs act in a different and complementary manner to metformin.

## What is the role of combination therapy in diabetes?<sup>20,21</sup>

### Oral agents and Insulin

The new, evolving treatment paradigm may well be to initiate combination therapy right from the onset of diabetes to address the pathogenic defects and to promptly add supplemental insulin therapy if glycemic goals are not achieved. Thus, despite the increasing array of oral agents, insulin therapy will eventually be required because of a gradual decrease in pancreatic B-cell function. The fundamental issue is which regimen will achieve the target HbA<sub>1c</sub> of <7%. In contrast to oral therapy, insulin doses can be increased and adjusted until target reductions in HbA<sub>1c</sub> are achieved. However, the rate limiting factor for the use of increasing insulin dosages remains the risk of severe hypoglycemia, which was relatively low at 2.3% in the UKPDS. Studies are under way with experimental long-acting insulin analogues, with a more predictable, smooth, and peakless 24 hour profile, that may provide the basal insulin needed for combination strategies with less risk of hypoglycemia.

Glimepiride, metformin, pioglitazone, troglitazone and acarbose are the only agents currently approved by the FDA for combination use with insulin. In the combination therapy, insulin 70/30 at dinner is added to pre-existing oral therapy, either to control fasting hyperglycemia or to ease the transition from oral sulphonylurea treatment to insulin. Adding insulin in the evening is a simple and effective strategy that can be regarded as 'bridge therapy'. It allows patients to overcome their initial resistance to starting using insulin, especially when administered with an insulin pen, facilitating long term acceptance and compliance, if further intensive insulin therapy is required.

### Conclusions

The goals of glycemic control have been defined in large prospective studies and their beneficial effects documented as regards diabetes-related complications. The recent developments in modalities of treatment, insulin analogues short and long acting, will

help obtain better glycemic profiles for Type 1 and 2 diabetic patients, with less risk of severe hypoglycemia.

The newer oral hypoglycemic agents will help in targeting various defective sites which form the basis of Type 2 diabetes pathogenesis. Therefore, planning treatment will have a rational approach, either targeting insulin secretion throughout 24 hours, or post-meal, and/or increasing peripheral glucose utilization by insulin sensitizers. Combination therapy in Type 2 diabetes mellitus will offer better future management of Type 2 diabetes.

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### MCQs for CME

After you have completed reading the above article, take the test given below. Circle T (True) or F (False) in the answer sheet (page 36) to show the correct answer to each MCQ. MCQs 1 to 10 are related to the content in this article.

1. Based on the DCCT results there was a significant reduction of retinopathy.
2. Extrapolation of the DCCT results to adult Type 2 diabetes mellitus is impossible.
3. Based on the UKPDS results intensive treatment policy achieved reduction of microvascular complications among Type 2 diabetic patients.
4. Blood pressure control among Type 2 diabetic patients had no effect on risk reduction on diabetes related deaths.
5. Insulin analogues (insulin lispro and aspart) are more rapidly absorbed after subcutaneous injection and achieving peak plasma concentration twice as high compared to regular insulin.
6. Insulin glargine has prolonged duration of action and is associated with less nocturnal hypoglycemia.
7. New sulphonylurea compounds e.g. Glicazide MR have no effect on cardiac ATP channels.
8. The meal oriented short lived effect of repaglinide target fasting hyperglycemia.
9. Thiazalidinediones (TZDs) provide a new means of glycemic control by reducing insulin resistance.
10. Thiazalidinediones (TZDs) are contraindicated in diabetic patients with cardiac failure and/or with impaired liver function.