NIDDM: a rapid progressive disease
Results from a long-term, randomised, comparative study of insulin or sulphonylurea treatment

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Summary The objective of the present study was to assess the relative efficacy of insulin or glibenclamide treatment for non-insulin-dependent diabetes mellitus (NIDDM) over 42 months. We performed a randomised, controlled trial allocating patients treated with diet and oral antihyperglycaemic agents to treatment with glibenclamide or insulin to achieve HbA_{1c} levels under 7.5 %. We included 36 subjects with established NIDDM of more than 2 years' duration. Mean HbA_{1c} levels were significantly reduced in patients allocated to insulin treatment from $9.1 \pm 1.4 \%$ before the start to $7.8 \pm 1.3 \%$ ($p < 0.05$) after 1 year, and did not change significantly thereafter throughout the study period. Mean HbA_{1c} levels increased during the study in the patients allocated to glibenclamide treatment, and 11 of 18 patients had to be switched to insulin treatment due to increasing hyperglycaemia ($HbA_{1c} > 10 \%$). Mean body weight increased in the subjects allocated to insulin by 7.2 ± 4.1 kg during the study period. In conclusion, insulin was more effective than glibenclamide treatment in obtaining control over hyperglycaemia in these patients, and once improved, glycaemic control did not deteriorate over 42 months in the insulin-treated group. Two thirds of the patients allocated to glibenclamide treatment had to be given insulin due to inadequate glycaemic control. [Diabetologia (1996) 39: 1629–1633]

Keywords Insulin treatment, sulphonylurea treatment, metabolic control.

Recently published studies indicate that good glycaemic control is important for the rate of progression of microvascular complications and possibly also for macrovascular complications in non-insulin-dependent diabetes mellitus (NIDDM) [1–6]. It is therefore important to use the most efficient blood glucose lowering therapy for patients with this disease. While diet, oral agents and insulin seem equally effective in controlling hyperglycaemia during the first year after diagnosis [7], longer follow-up of NIDDM patients shows a progression of hyperglycaemia both in diet-treated and in orally treated subjects [8, 9]. The results from the 3.5 and 6 year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) [10, 11] seem to indicate that there is a trend towards increasing levels of HbA_{1c} after the initial reduction seen in all the treatment groups during the first year.

The OCTOPUS study (Oslo Comparative Trial of Peroral vs Insulin Treatment in Type 2 diabetes) is a prospective, long-term, randomised study to compare the effects of insulin and sulphonylurea (SU) treatment in NIDDM patients with established disease. The main endpoint to be evaluated after 5 years is retinopathy status, but several secondary endpoints including nephropathy, macrovascular disease and metabolic profile will also be evaluated. The present report gives the 3.5 year follow-up status of metabolic control in the first 36 subjects included in this study. We have previously published baseline data and 12 months' follow-up data in these patients [12].

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Table 1. HbA$_{1c}$ fasting plasma glucose and body weight at baseline and after 42 months of treatment in the patients randomised to insulin or sulphonylurea treatment

	Insulin		Sulphonylurea		
	Start	42 months	Start	End-of-tablet	42 months
HbA$_{1c}$ (%)	9.1 ± 1.4	8.2 ± 1.0^a	8.5 ± 1.4	$10.2 \pm 1.6^{b, c}$	8.4 ± 1.2
Fasting plasma glucose (mmol l^{-1})	11.6 ± 3.2	8.0 ± 2.9^b	11.4 ± 2.3	12.1 ± 3.1^c	8.9 ± 3.8^a
Weight (kg)	75.3 ± 13.2	82.4 ± 14.5^b	76.8 ± 13.9	75.4 ± 13.5	78.2 ± 12.1^a

Values are mean $\pm$ SD.
[a] $p < 0.05$ vs start; [b] $p < 0.01$ vs start; [c] $p < 0.05$ vs insulin.

The "end-of-tablet" values are measurements performed in the SU-treated patients at the last visit before changing to insulin therapy, or, for those who remained on SU, at 42 months

Subjects, materials and methods

Twenty-two men and 14 women aged 59.2 ± 6.1 years (mean $\pm$ SD) with a known NIDDM duration of 7.6 ± 2.8 years and with an initial HbA$_{1c}$ level of 7–10%, were studied. After a run-in period of at least 3 months with stable glycaemic control on diet alone (two subjects) or in combination with glibenclamide (1.75–10.5 mg micronized formulation of Daonil; Hoechst AG, Frankfurt, Germany), they were randomly assigned to treatment with insulin ($n = 18$) or glibenclamide ($n = 18$). Mean body mass index (BMI) in the insulin group was 26.4 ± 3.1 kg $\cdot$ m^{-2} and in the SU group 26.2 ± 3.8 kg $\cdot$ m^{-2}, and 17 of the patients had a BMI over 26 kg $\cdot$ m^{-2}. All patients had post-glucagon C-peptide levels over 0.7 nmol $\cdot$ l^{-1}. Insulin therapy was started in the outpatient clinic, with an injection of 8 IU of intermediate acting (NPH) insulin at 08.00 hours and 22.00 hours. The insulin dose was adjusted subsequently during frequent visits to the outpatient clinic or by telephone contact with the patients to achieve near-normoglycaemia, aiming at a fasting blood glucose concentration below 7 mmol $\cdot$ l^{-1} and a postprandial blood glucose concentration below 10 mmol $\cdot$l^{-1}. Six patients were subsequently changed to a multiple-dose regimen (regular insulin 30 min before each meal and intermediate acting insulin at 22.00 hours), because of inadequate metabolic control with the two-dose regimen. The maximal dose of glibenclamide given was 10.5 mg per day (7 mg before breakfast and 3.5 mg before dinner), and the dose was adjusted with the same goals for glycaemic control as for insulin. Initially, the protocol specified a change to insulin therapy in the patients randomised to oral treatment if HbA$_{1c}$ exceeded 11%. However, as evidence was accumulating in the literature that very poor glycaemic control might be harmful, this limit was changed, to HbA$_{1c}$ above 10% 1 year after randomisation of the first patients, in an amendment to the protocol.

The study was approved by the regional ethical committee, and all participants gave written informed consent for participation.

Patients were evaluated every 3 months, with recordings of weight and blood pressure (measured in the sitting position after 5 min rest, Korotkoff's phase 1 and 5 recorded) and blood sampling for determination of glucose and HbA$_{1c}$ and also every 6 months for fasting levels of cholesterol, HDL-cholesterol and triglycerides. Eleven subjects in the SU-group had to be withdrawn from the study and given insulin due to increasing HbA$_{1c}$ levels above the limits specified in the protocol or to symptomatic hyperglycaemia. One patient in the insulin group died from a myocardial infarction after 24 months, and one patient in the SU group withdrew from the study after 12 months.

Laboratory analyses. The plasma concentration of glucose was measured by the glucose oxidase method using a Beckman glucose analyzer (Beckman Instruments, Inc., Fullerton, Calif., USA). HbA$_{1c}$ was determined by high performance liquid chromatography using an automatic DIAMAT HbA$_{1c}$ analyzer (Bio-Rad Laboratories, München, Germany, intra- and inter-assay coefficient of variation (CV) < 3%) and during the last year by an immunological method (BM Tinaquant; Boehringer Mannheim, Mannheim, Germany, CV < 9%). Normal range for HbA$_{1c}$ in non-diabetic subjects is 4.3–6.1% using the DIAMAT. Simultaneous measurements of HbA$_{1c}$ with the two methods showed that HbA$_{1c Tinaquant}$ = 1.1 HbA$_{1c DIAMAT}$ – 1.7, and values obtained by immunoassay were adjusted using this algorithm. Cholesterol and triglycerides were measured at the Department of Clinical Chemistry, Aker Hospital using a Hitachi 737 multianalyzer with chemicals from Boehringer Mannheim. HDL-cholesterol was measured at the Department of Clinical Chemistry, Ullevål Hospital, Oslo, as cholesterol in the supernatant after precipitation with heparin/manganese chloride using a Cobas Bio centrifugal analyzer (Roche Diagnostica, Basel, Switzerland).

Statistical analysis

Values are given as mean $\pm$ SD. Skewed data were log-transformed before calculating the mean. Paired and unpaired t-tests were used for comparisons, and Pearson's correlation coefficient was calculated. A significance level of 5% was used. The two groups were compared after 42 months of treatment according to randomisation (intention to treat). However, as 11 of 18 patients randomised to SU had to be given insulin, comparisons were also performed between the insulin group at 42 months and the patients randomised to SU at the last visit before they changed to insulin therapy, or – for those who did not change therapy – at 42 months ("end-of-tablet period"). Finally, the five patients remaining on tablets throughout the study were also evaluated separately.

Results

The mean HbA$_{1c}$ level was similar in the insulin and the SU group at the start of the study (9.1 ± 1.4 and 8.5 ± 1.4%, respectively, $p = $ NS). HbA$_{1c}$ fell significantly in the patients allocated to insulin and remained lower throughout the study period (Table 1). In the SU group, the mean HbA$_{1c}$ at 42 months was not significantly different from the start. However, the mean HbA$_{1c}$ level at the "end-of-tablet period" was significantly increased (10.2 ± 1.6%) as compared to the level at the start, $p < 0.01$ and also as compared to the level in the insulin group at 42 months, $p < 0.05$.

Table 2. Values for lipids at baseline and after 42 months of treatment in the patients randomised to insulin or sulphonylurea treatment

	Insulin		Sulphonylurea		
	Start	42 months	Start	End-of-tablet	42 months
Triglycerides (mmol · l^{-1})	1.8 ± 0.8	1.6 ± 0.8	1.8 ± 1.0	1.7 ± 1.2	1.5 ± 0.9
Cholesterol (mmol · l^{-1})	6.8 ± 0.4	6.3 ± 1.6	6.4 ± 1.1	6.5 ± 1.2	6.4 ± 1.0
HDL-cholesterol (mmol · l^{-1})	1.37 ± 0.3	1.28 ± 0.4	1.28 ± 0.4	1.10 ± 0.3[a]	1.18 ± 0.4

Values are mean ± SD.
[a] $p < 0.05$ vs start

The "end-of-tablet" values are measurements performed in the SU-treated patients at the last visit before changing to insulin therapy, or, for those who remained on SU, at 42 months
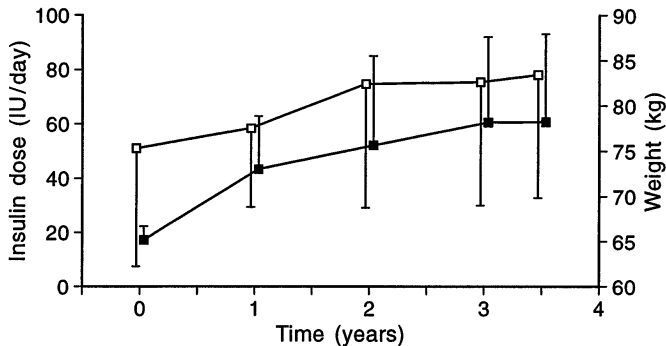

Fig. 1. Insulin doses (■) and body weight (□) during the study in patients randomised to insulin treatment. Mean ± SD.
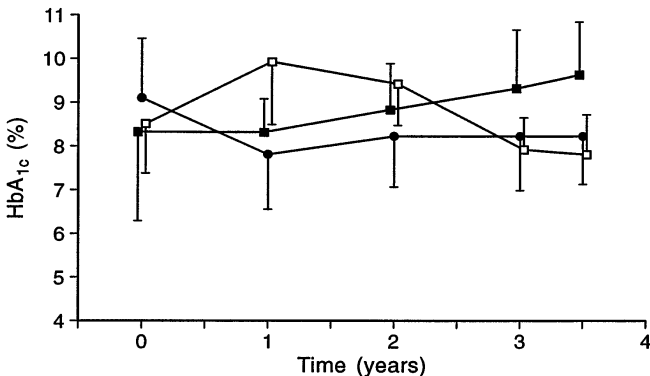

Fig. 2. Levels of HbA$_{1c}$ in patients randomised to insulin (●); patients randomised to SU and subsequently changed to insulin (□) and patients randomised to and remaining on SU (■). Mean ± SD

The mean fasting blood glucose levels fell significantly both in the insulin and in the SU group during 42 months' treatment, but was not significantly different between the groups (Table 1). However, the fasting glucose level was higher in the SU group at the "end-of-tablet period" when compared to the level at 42 months in the insulin group ($p < 0.05$).

Mean body weight increased significantly during treatment in the insulin group (75.3 ± 13.2 to 82.4 ± 14.5 kg, $p < 0.01$), which paralleled the increase in insulin dose (Fig. 1). There was also a slight increase in mean weight in the SU group at 42 months, but not at the "end-of-tablet period".

Only small and mostly insignificant changes were observed in lipid levels throughout the study period (Table 2). There was a non-significant trend to a reduction in the mean levels of triglycerides and cholesterol in the insulin group (1.8 ± 0.8 to 1.6 ± 0.8 mmol/l, $p = 0.06$, and 6.8 ± 0.4 to 6.3 ± 0.4 mmol/l, $p = 0.09$, respectively). The mean level of HDL-cholesterol fell in the SU group as the glycaemic control deteriorated from start to the "end-of-tablet period" (1.28 ± 0.4 to 1.10 ± 0.3 mmol/l, $p < 0.05$).

No changes were observed in systolic or diastolic blood pressures in any of the groups during the study period (data not shown). However, in the insulin group two patients started antihypertensive medication and two patients increased the doses of antihypertensive treatment during the 3.5-year follow-up.

When glycaemic control was evaluated in the patients who remained on SU treatment, there was a clear tendency to increase in mean HbA$_{1c}$ level throughout the study period (Fig. 2). These subjects had slightly longer duration of diabetes at baseline compared to the 11 patients in the SU group that had to be given insulin (10.2 ± 3.1 vs 6.8 ± 3.2 years, $p = 0.07$).

Post-glucagon C-peptide levels at baseline correlated significantly and negatively to average HbA$_{1c}$ after randomisation (r = –0.37, $p = 0.03$).

Discussion

The deterioration of metabolic control leading to therapeutic failure is a common problem in patients with NIDDM, and is well known from previous studies [13–16]. However the magnitude of the problem is not well understood, due to lack of long-term, randomised and prospective studies. Clauson and co-workers [16] found in a cross-sectional study from Sweden that 60 % of patients with NIDDM of more, than 15 years' duration, used insulin [16]. In agreement with data from the UKPDS [11], they also found that increasing beta-cell insufficiency was the most likely explanation for the progression of the disease. It is therefore of interest that post-glucagon C-peptide values at baseline in our study correlated negatively to metabolic control during the study, and

therefore to a certain extent were predictive for the metabolic control that could be achieved.

Hence, the most important finding in our study is the rapid deterioration of glycaemic control that we observed in our SU-treated patients. This suggests that hyperglycaemia is not a stable condition, but progressively increases in nearly all these patients, demanding close monitoring and aggressive treatment if near-normoglycaemia is the therapeutic goal. An essential question in the interpretation of the present results is the selection of the study population. All the patients had known NIDDM for several years prior to inclusion, and had at least partly preserved beta-cell function. The mean duration of diabetes at inclusion in this population was 7.6 years, but it is known that many patients with NIDDM have had their disease for several years before diagnosis [17]. It is therefore likely that a majority of patients in our study had the disease for 10 years or more at inclusion. This is important when comparing the results to other recently published studies. Niskanen et al. [9] found a gradual deterioration of insulin response to oral glucose stimulus during a 10-year follow-up of newly diagnosed NIDDM patients [9]. Only 7 % of the patients required insulin treatment after 10 years, however, the mean HbA_{1c} level in patients on oral treatment was 9.5 % and the authors do not specify the indications for changing to insulin treatment. The patients included in the UK-PDS were also newly diagnosed, and 6-year follow-up data showed gradually increasing glucose levels [11]. However, probably due to shorter duration of the disease, the mean levels of fasting plasma glucose and HbA_{1c} are still considerably lower than in our study. In contrast to the finding in the UKPDS, our insulin-treated patients had a stable HbA_{1c} throughout the study period. This may be due to the small scale of our study with close follow-up of the patients and the use of intermediate-acting and regular insulin to best match the needs of the individual patient.

Body weight increased during insulin treatment, and the increase seems to parallel the increase in insulin doses, levelling off after 2 years (Fig. 2). We have previously shown that about 30 % of the weight increase in the first year of insulin treatment was due to an increase in lean body mass [12]. We, and others, have also shown that there are significant intercorrelations between body mass, insulin resistance, and the levels of blood pressure, triglycerides and HDL-cholesterol in NIDDM [12, 18]. Hence the considerable increase in body weight observed during insulin treatment may be counterproductive with respect to several components of the insulin-resistance syndrome. It may also in part explain the lack of a beneficial effect on triglyceride (and HDL-cholesterol) levels that would have been expected to follow improvement in metabolic control [19, 20].

The mechanisms leading to deterioration of metabolic control with duration of hyperglycaemia in these patients is not fully elucidated. It may be due to an increase in insulin resistance or diminishing insulin secretion with the duration of hyperglycaemia [21, 22]. Both these phenomena have been suggested to result from long-standing hyperglycaemia per se (glucotoxicity) [23]. However, Groop et al. [15] found that only 56 % of the failures to SU therapy could be explained by the combination of hepatic and peripheral insulin resistance and insulin deficiency.

In a majority of our patients with NIDDM of long duration, we were not able to maintain acceptable metabolic control with diet and SU treatment. Insulin treatment managed to maintain acceptable glycaemic control during 3.5-year follow-up, but at the cost of a significant increase in body weight.

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