Adherence to insulin and its association with glycaemic control in patients with type 2 diabetes

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Summary

Background: Good glycaemic control improves outcomes in patients with type 2 diabetes, but the extent to which this depends on adherence to insulin treatment is uncertain.

Aim: To investigate the association between adherence to insulin and glycaemic control in insulin-treated patients with type 2 diabetes.

Design: Observational records-based study.

Methods: We studied all patients with type 2 diabetes who were resident in Tayside, Scotland from 1 January 1995 to 30 September 2001, and who were treated with insulin. Adherence to insulin treatment was measured as the annual number of days of insulin coverage on the recommended dose, calculated from the amount of drug dispensed at community pharmacies and the recommended dose level for each patient. The association between glycaemic control (HbA\textsubscript{1c}), and adherence was determined, as was the influence of covariates, including age, sex, duration of diabetes and number of injections per day.

Results: A total of 1099 people were studied: 574 (52%) males and 525 (48%) females, mean ± SD age 62 ± 12 years, diabetes duration 10 ± 7 years. Median time in the study (time for which insulin was dispensed) was 1107 (range 366–2446) days. Insulin prescribed was 58.0 ± 33.3 IU/day and insulin collected from pharmacies was 53.6 ± 27.1 IU/day. Mean adherence to insulin was thus 70.6% ± 17.7%.

Adherence to insulin (\textit{p} = 0.0021), BMI (\textit{p} = 0.0001) and diabetes duration (\textit{p} = 0.0314) were all significant predictors of HbA\textsubscript{1c}.

Discussion: Adherence to insulin appears poor in these type 2 diabetes patients, and there was a significant relationship between adherence and long-term metabolic control.

Introduction

Improved glycaemic control in people with diabetes reduces the risk of long-term complications.\textsuperscript{1,2} In the DCCT (Diabetes Control and Complications Trial), good control of HbA\textsubscript{1c} in patients with type 1 diabetes was associated with reduced risk of retinopathy, neuropathy and nephropathy,\textsuperscript{1–5} and the UKPDS (United Kingdom Prospective Diabetes Study) has provided evidence for the benefits of tight glycaemic control and blood pressure control in patients with type 2 diabetes.\textsuperscript{6} Application of the DCCT statistical methodology to patients with type 2 diabetes suggests a 24% reduction in the relative risk of retinopathy for every 10% decrease in HbA\textsubscript{1c}.\textsuperscript{7}

Poor adherence to the diabetic regimen is widely acknowledged as a potential cause of poor metabolic control,\textsuperscript{8} but further research is needed to quantify the specific improvement in glycaemic control that might be obtained from better adherence to insulin. We have previously shown an inverse association between an index of adherence to insulin and HbA\textsubscript{1c} in insulin-treated patients with type 1 diabetes (\textit{R\textsuperscript{2} = 0.39; p < 0.001}).\textsuperscript{9} Among patients with an HbA\textsubscript{1c} measurement in the top
quartile (HbA1c >10.5%), 14 (64%) individuals had an adherence index suggestive of a missed dose of insulin (mean deficit 55 insulin days/annum). Two large cohort studies of adherence to insulin in type 2 diabetes, and reported adherence rates of 63%±24% and 77%±17%, respectively.10,11 However, to the best of our knowledge, only one study has investigated the relationship between adherence and glycaemic control in older patients with type 2 diabetes, and they found a significant inverse relationship between the two.11 The aim of this population-based study was investigate the association between adherence to insulin treatment and glycaemic control in all patients with type 2 diabetes.

Methods

Data sources

This study used the resources of the DARTS/MEMO Collaboration. DARTS (Diabetes Audit and Research in Tayside) is a validated population-based diabetes information system for the population of Tayside, Scotland (population ~400 000). It is compiled by record-linking several independent data sources, including hospital admissions, diabetes clinic visits and diabetic medication, using a unique health-care identifier assigned to patients when they register with a General Practitioner. It has high sensitivity (97%) for identifying patients with diabetes and has been described in detail previously.12 Within the DARTS system, patients are diagnosed with type 1 diabetes if they are aged 0–35 years at diagnosis, and either insulin-treated, or initially treated with oral hypoglycaemics or diet alone, but progress to insulin within 1 month. Patients under the age of 35 years who do not require insulin are diagnosed as having type 2 diabetes, as are all patients diagnosed over the age of 35 years, irrespective of treatment. The prevalences of type 1 and type 2 diabetes in Tayside are 0.4% and 3.1%, respectively.13

The dispensed prescribing database of the Medicines Monitoring Unit (MEMO) was also used in this study.14 The MEMO database was developed for pharmacoepidemiological research in the population of Tayside, and contains detailed records of all prescription items dispensed to patients in community pharmacies. Thus for all diabetic patients in Tayside, there are records of all prescriptions dispensed for insulin and other diabetic medication.

Study population

The study population included all residents of Tayside, Scotland, who were diagnosed with type 2 diabetes and also treated with insulin prior to or during the study period 1 January 1995 to 30 September 2001. Those who moved from Tayside within the study period were excluded. Patients were also excluded if they had no medically recommended dose (this information was limited to patients resident in Dundee, the major centre in Tayside). In addition, patients were excluded if there were no HbA1c measurements recorded during the study period or if insulin use was for <12 months.

The study start date for each patient was defined as the date of their first insulin prescription dispensed at a community pharmacy on or after 1 January 1995. The end date was the date of the last insulin prescription dispensed before 30 September 2001. Therefore the maximum follow-up period was 6.75 years.

Calculation of adherence

For each prescription of insulin received in the population, we knew the strength and the amount dispensed. We derived the medically recommended insulin dosage prescribed over the study period (calculated as the mean of the doctors’ or diabetes specialist nurses recommendations at each clinic visit) from records kept by Diabetes Specialist Nurses and physicians during clinical appointments or opportunistic specialist nursing telephone review. This allowed us to calculate the intended duration of every insulin prescription. If subsequent prescriptions were dispensed before the end of a previous prescription, the previous prescription was censored at the start of the new prescription. Therefore the maximum possible adherence for each patient was 100%. The total number of days of drug coverage was then summed (excluding the last prescription) and divided by the total follow-up in the study (in days), to yield a percentage. In addition, we searched the SMR1 database for any hospital admissions to Tayside hospitals during the study period. Any time spent as an in-patient was assumed to have drug coverage supplied by the hospital, as this is standard procedure in Tayside, and therefore these days of drug coverage were added to the total obtained from community prescribing when calculating the adherence index.

Glycaemic control

Glycaemic control was assessed using all the HbA1c concentrations recorded during the study period for each individual.
Statistical analysis

The characteristics of the study population were summarized by means and standard deviations for continuous measurements and as percentages for categorical factors. Patient characteristics were segregated by adherence, using 80% as a cut-off.\textsuperscript{15} Comparison between groups was by \chi^2 for categorical variables and t-tests for continuous variables.

Each patient had several HbA\textsubscript{1c} measurements taken during the study; this information was thus incorporated into a longitudinal model, rather than using a mean or dichotomizing the dependent variable. Therefore, a linear mixed-effects regression model was used to analyse the effects of adherence on HbA\textsubscript{1c}.\textsuperscript{16} The mixed-effects regression model easily accommodates unbalanced, unequally spaced observations, and is therefore an ideal tool for use in an observational dataset.\textsuperscript{17} In the mixed-effects model, estimates of the longitudinal changes in HbA\textsubscript{1c} levels are represented by the follow-up time (time and time squared) and its interactions. The variables included in the model were: adherence, an interaction between adherence and time, age at baseline, diabetes duration, time and time squared, body mass index (BMI), gender, frequency of insulin administration and a postcode measure of material deprivation derived from the UK census.\textsuperscript{18,19} This is measured on a scale of 1 to 7, with 1 being least deprived and 7 most deprived.

Three random effects were included in the model: intercept, time and time squared. These random effects allow the patient’s baseline measurement to vary from the study population average (intercept) and the longitudinal trajectory for both the linear (time) and quadratic (time squared) variables to vary from the population average. All analyses used SAS (v. 8.2).

Results

In the population of approximately 5102 patients with type 2 diabetes in Tayside, Scotland, 3770 (74\%) were treated with insulin during the study period. A total of 2671 (71\%) patients were excluded from the study due to lack of information about their prescribed insulin dose, absence of HbA\textsubscript{1c} measurements, or insulin use for <12 months, leaving 1099 who met the final study criteria (Figure 1).

The demographic characteristics and diabetes treatment details are shown in Table 1. Of the 1099 patients, 52\% were male. Mean ± SD age was 62 ± 12 years, with an age at diagnosis of 52 ± 12 years. BMI was 29.7 ± 5.9 kg/m\textsuperscript{2}; HbA\textsubscript{1c} was 8.5\% ± 1.3\%. Median length of time in the study (difference between start and end date) was 1107 days. On average, patients collected one prescription every 64 days. The mean ± SD number of HbA\textsubscript{1c} recordings during the study period was 9.2 ± 5.8. Overall, the volume of insulin prescribed was 58.0 ± 33.3 IU/day and the volume of insulin collected from pharmacies was 53.6 ± 27.1 IU/day. This equated to a mean ± SD adherence index of 70.6\% ± 17.7\% (range 8.2–100\%). Figure 2 shows the distribution of adherence.

Patients were segregated by adherence using an 80\% cut-off point. Patients with better adherence were older, with an older age of diabetes diagnosis, less socially deprived, with a lower BMI and HbA\textsubscript{1c} (Table 1). In addition, they were prescribed lower doses of insulin and a greater percentage were on a regimen of one injection per day. There were no differences by gender or diabetes duration.

The results of the mixed-effects linear regression are shown in Table 2. There was a significant inverse association between log adherence (\(p<0.0001\)) and HbA\textsubscript{1c}. HbA\textsubscript{1c} increased over time, demonstrating a significant quadratic trend (\(p=0.0023\)), accompanied by a significant linear trend (\(p<0.0001\)). This indicates some non-linear variation (e.g. HbA\textsubscript{1c} may level off or change direction over time) in addition to a linear trend. Patients with a higher BMI (and those with a longer duration of diabetes) had higher HbA\textsubscript{1c} levels. In addition, there was a significant interaction between adherence and time, suggesting longitudinal changes in HbA\textsubscript{1c} varied according to adherence (\(p<0.0001\)). This suggests that in patients with insulin-treated type 2 diabetes, improved adherence to insulin, shorter diabetes duration and lower BMI are associated with improved glycaemic control. No association was found for gender, age, number of daily injections or social deprivation (results not shown).
Discussion

This study confirmed low levels of adherence to insulin among patients with type 2 diabetes, with patients collecting on average 71% of their recommended dose from pharmacies. This finding is slightly higher than in a study by Rajagopalan et al., who reported an adherence rate of 63% ± 24% in patients with insulin-treated type 2 diabetes,10 and slightly lower than that of Cramer et al., who reported an adherence rate of 77% ± 17%.11

In a mixed-effect linear regression model, better adherence to insulin, lower BMI and shorter diabetes duration were all associated with lower HbA1c. In addition, HbA1c levels increased over time, and this varied depending on adherence level. Therefore improved adherence to insulin is associated with better glycaemic control. However, there was no association between improved glycaemic control and gender, age, number of daily injections or social deprivation.

Table 1  Demographic characteristics and diabetes treatment details and segregated by adherence

<table>
<thead>
<tr>
<th>Demographic details</th>
<th>All (n = 1099)</th>
<th>Adherence &lt;80% (n = 737)</th>
<th>Adherence ≥80% (n = 362)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline (years)</td>
<td>61.5 (11.9)</td>
<td>60.7 (11.6)</td>
<td>63.4 (12.1)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.0966</td>
</tr>
<tr>
<td>Males</td>
<td>574 (52.2)</td>
<td>365 (49.5)</td>
<td>160 (44.2)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>525 (47.8)</td>
<td>372 (50.5)</td>
<td>202 (55.8)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.7 (5.9)</td>
<td>30.0 (5.8)</td>
<td>29.1 (6.0)</td>
<td>0.0188</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.5 (1.3)</td>
<td>8.7 (1.3)</td>
<td>8.1 (1.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Carstairs deprivation score</td>
<td></td>
<td></td>
<td></td>
<td>0.0205</td>
</tr>
<tr>
<td>1</td>
<td>86 (7.8)</td>
<td>57 (7.7)</td>
<td>29 (8.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>151 (13.7)</td>
<td>92 (12.5)</td>
<td>59 (16.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>237 (21.6)</td>
<td>157 (21.3)</td>
<td>80 (22.1)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>233 (21.2)</td>
<td>156 (21.2)</td>
<td>77 (21.3)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>105 (9.6)</td>
<td>86 (11.7)</td>
<td>19 (5.3)</td>
<td></td>
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<tr>
<td>6</td>
<td>287 (26.1)</td>
<td>189 (25.6)</td>
<td>98 (27.1)</td>
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Diabetes treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Standard error</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>9.2175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log adherence</td>
<td>1.2172</td>
<td>0.2410</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time</td>
<td>0.0157</td>
<td>0.0051</td>
<td>0.0022</td>
</tr>
<tr>
<td>Time squared</td>
<td>−0.4294</td>
<td>0.1396</td>
<td>0.0021</td>
</tr>
<tr>
<td>BMI</td>
<td>0.0268</td>
<td>0.0070</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>0.0119</td>
<td>0.0055</td>
<td>0.0314</td>
</tr>
<tr>
<td>Time × adherence</td>
<td>−0.2722</td>
<td>0.0569</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Our patients who were poorly adherent were prescribed significantly higher doses of insulin (66.4 ± 34.6 IU/day in patients with <80% adherence vs. 40.8 ± 21.9 in patients with ≥80% adherence, p<0.0001), which might reflect a tendency for health-care professionals to suggest an increased dose in an attempt to improve HbA1c in the context of poor adherence. Injection frequency was also associated with adherence. There was a inverse linear relationship between adherence and number of injections: patients requiring only one injection per day had adherence 78.3% ± 17.8%, vs. 60.8% ± 21.7% (p<0.0001) in patients requiring four injections per day. This finding is consistent with a study by Donnan et al., who found that poorer adherence to oral hypoglycaemic medication was associated with an increase in daily number of tablets prescribed.20

This study is limited by the generalizability of its results. Comparing the study population with those excluded (n=2671) due to lack of information about their prescribed dose, absence of HbA1c measurements, or short insulin duration (<1 year), excluded patients were significantly younger, with longer diabetes duration, and the pattern of daily injections was significantly different, with a larger percentage of patients on one and four injections per day. The reason for exclusion for a majority of the patients was absence of HbA1c measurements. These patients may have attended diabetes clinics less frequently and may be a less adherent group than those included in the study. If so, poor adherence may have been underestimated in the study.

Adherence is very difficult to measure accurately.21 Our calculation was based on an average for patients during the study period, and was therefore insensitive to temporal variations. We have no information on the day-to-day variability of insulin regimens, and it may be (for example) that some patients were using a fast-acting insulin on a sliding scale basis. In addition, we were unable to establish what proportion of insulin dispensed went unused by the patient. Similarly, patients may have hoarded insulin prior to the study start date, or injected more insulin than instructed in an attempt to achieve better control.

Our study used a validated diabetes database. Data on insulin collected came from a database of prescriptions dispensed.14 Prescriptions issued within Tayside are collected, almost exclusively at Tayside pharmacies,22 so it is unlikely that significant amounts of insulin were obtained outside Tayside. We were also able to obtain information on insulin prescribed for many patients attending diabetes clinics and those being looked after in the community, as diabetes nurse specialists have a region-wide responsibility.

This study is one of only a few to evaluate the association between adherence to insulin and glycaemic control in type 2 diabetes. Ascertainment of drug coverage was reliable, as complete population-based information on all drugs dispensed at pharmacies in Tayside was available. This was an observational study, with the patients unaware that they were being studied, so their behaviour was not modified in any way by the study. This is a major drawback of methods such as the Medication Event Monitoring System (MEMS).23

In conclusion, our results suggest that over one third of patients with type 2 diabetes are poorly adherent to their diabetic regimen, and that this has significant implications for glycaemic control. Poor patient adherence continues to be a problem in health-care delivery.

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References


