Improvements in glycaemic control and cardiovascular risk factors in a cohort of patients with type 1 diabetes over a 5-year period

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Summary

Background: Management of patients with type 1 diabetes in the UK has changed over the past 20 years. The targets for glycaemic control, blood pressure and cholesterol are lower. We examined a cohort of patients with type 1 diabetes who have been through these changes to assess their effects.

Design and Methods: A cohort of patients with type 1 diabetes who attended a secondary care outpatient diabetes clinic between 1991 and 1996 were reviewed in 2001 and 2006. Comparison is made between current biophysical markers and those obtained in 2001.

Results: Only 81.9% (n=214) of the original cohort attended in 2006. These patients had an average duration of diabetes of 23.46 (SD ± 8.06) years. There were 134 male patients (62.62%). In these patients HbA1c had reduced by 0.4% (absolute reduction); a relative reduction of 4.41% (P=0.0001). Statistically significant reductions in diastolic blood pressure (74–68 mmHg) and total cholesterol (5.37–4.62 mmol/l) occurred. However, weight (75.04–82.31 kg) and BMI (25.32–27.72 kg/m²) significantly increased. There was no statistically significant change in insulin dose (units/kg), serum creatinine, urinary ACR or systolic blood pressure.

Conclusions: An urban setting, mobile population and patient non-attendance can complicate modern diabetes care. Despite these difficulties, input by the diabetes team working with the patients can achieve small improvements in HbA1c and cardiovascular risk factors by increased use of long acting insulins, metformin, statins and blood pressure medication.

Introduction

The care of patients with diabetes has changed considerably in the past decade. Developments have lead to the increased use of analogue insulin, particularly in patients with type 1 diabetes (T1DM), the use of the insulin pen,¹ continuous subcutaneous insulin infusion (CSII)² and more recently inhaled devices.³ There has also been change in diabetes education programmes and the integration of this with adjustment of both diet and insulin dose.⁴

In tandem with a more patient centred approach, such changes would hope to improve the quality of life of patients and decrease the risk of complications of diabetes by improving glycaemic control. The landmark Diabetes Control and
Complications Trial demonstrated this and served to focus services on the importance of glycaemic control in the prevention of complications of diabetes.

Furthermore, modifiable cardiovascular risk factors, such as serum cholesterol and blood pressure have come under increased scrutiny and led to a series of guidelines being published and ‘target’ values being recommended; these targets have become increasingly tight over the last few years as evidence accumulates of the benefits of risk factor control.

It was therefore felt appropriate to assess what effect, if any, these changes have had on the care of a cohort of patients with T1DM who have been attending the same Diabetes outpatient clinic since before and through many of these developments.

**Methods**

A previous assessment had been made of this cohort of patients in 2001 who were long term attendees of the clinic. Due to the evolving nature of diabetes care, the progression in technology and the increasingly pro-active treatment of cardiovascular risk factors, it was decided to review the remaining patients who were attending the same clinic in 2006 assessing what change, if any, had occurred in biophysical markers, medications and outcome in the intervening 5 years. The diabetes clinic has been led by the same Consultant Diabetologist and Diabetes Specialist Nurse (DSN) and nursing team since its inception. It has always had the support of a specialist diabetes dietician. Patients were offered a minimum of six monthly appointments with the medical team and those with poor glycaemic control were reviewed more frequently as determined by the medical team. Contact with the DSN team could be as frequent as every week if necessary and was determined by clinical need. Patients with poorly controlled cardiovascular risk factors were seen more frequently for blood pressure and lipid control.

Clearly as the evidence supporting tight glycaemic and aggressive risk factor management accumulated, over the period being examined, the nature of the care delivered in the clinic responded accordingly. More input was offered to achieve these targets and those patients not near ‘target’ were followed up more frequently by both medical and DSN teams.

In 2001 all previous clinic attendances of all eligible patients were reviewed. To be eligible these patients must have attended the clinic between 1991 and 1996 with at least two attendances. Biophysical data from each attendance was recorded. Average values for each variable of each patient were calculated during their period of follow-up. Data for the whole patient group was then presented as an average of these values. In early 2007, a review of the clinic attendances during the year ending 31 December 2006 was performed. Data from the last outpatient clinic attendance during 2006 was recorded. Current medication use was recorded; this was compared to the recorded medication from their last attendance in the previous review. Patients who were no longer attending the clinic, but who had been included in the earlier assessment were not reviewed here, although record was made of these patients.

**Statistical analyses**

All data was assessed for normality of distribution. Parametric data was analysed using Students’ t-test (matched or non-matched) where appropriate. Non-parametric data analysis was made using Mann–Whitney U-test. Comparison of use of medication was calculated using the test of significance on two independent proportions. Significance was taken to be a $P$ value of $<0.05$. All data analysed using StatsDirect version 2.6.5., StatsDirect, Cheshire, WA14 4QA, UK.

**Results**

Between 1991 and 1996, 386 patients attended at least once and had recorded biophysical data. There were 214 patients of the original cohort still attending the clinic by the end of December 2006 (Table 1).

**Non-Attendees**

Of the patients reviewed in 2001 five had died by 2006. Their average age at death being 58.8 (SD 12.78) years, and duration of diabetes 40.6 (SD 7.64) years. Thirty-four patients had either been discharged due to persistent non-attendance (28 patients) or had had their care transferred to another diabetes clinic or consultant (6 patients). A further eight patients were lost to follow-up by the clinic (Table 1).

**Continued attendees in 2006**

The 214 patients seen and reviewed in the year 2006 had an average age of 43.66 (SD 9.59) years and an average duration of diabetes of 23.45 (SD 8.06) years. The data described on these patients in 2001 was then compared with the 2006 data to see if any significant changes had occurred in the
intervening years. Table 2 shows the baseline data from both interval analyses and the statistical significance of any differences.

The results show that in the intervening period these 214 patients have seen a significant reduction in their mean HbA1c, diastolic blood pressure and total cholesterol. There was however a significant increase in their weight and body mass index over the same period. No significant change could be found in plasma creatinine levels, urinary ACR or systolic blood pressure. There was no significant change in the units of insulin used per kilogram of body weight during this time.

**Achievement of targets in 2006**

During the period preceding the 2001 data collection, the guidelines for management of patients with T1DM in the clinic were roughly based around the results of the DCCT study; that is to say, we strove for tight glycaemic control with the a target value of <7.8% higher than the normal range. Blood pressure management was aimed at the guidelines recommended in the then recently published Joint British Societies Guidelines, that is a systolic blood pressure of <130mmHg and a diastolic blood pressure of <80mmHg. Total cholesterol values were targeted at values of <5mmol/l. Although no guidelines were published as such, we aimed to maintain serum creatinine in the normal range, and as recommended screened annually for microalbuminuria (taken as >3.5mg/mmol in the data used here). Both of these are clearly influenced by glycaemic and blood pressure control. Details regarding the now more commonly used eGFR were not available for the original study, so comparison was kept as like-with-like and creatinine and ACR were used.

Ideally we also tried to maintain a normal body weight and BMI by encouragement of a healthy diet and exercise.

The proportion of the clinic patients achieving many of the targets in 2001 was less than ideal (Table 3). Gratifyingly a high proportion of patients reached the blood pressure targets. The majority of patients had normal mean ACR and mean creatinine. The proportions of the cohort achieving the targets in 2006 are also shown. The targets for systolic blood pressure remained unchanged over the review period and nearly two thirds of the cohort was still in the target range. The recommendation for diastolic blood pressure also remained the same, and the proportion of the cohort achieving it had increased from 84.58% to 93.93%. Similarly, even though the glycaemic target had dropped from <7% to <6.5%, more patients in the cohort were within the target range. The number of patients with a normal BMI had decreased over the intervening period for 107 to 63. A clear change in prescription

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**Table 1** The dispersal of a patient cohort attending a diabetes clinic between 1996–2006

<table>
<thead>
<tr>
<th>Year</th>
<th>Number attending</th>
<th>Defaulted from clinic/discharged</th>
<th>Moved away from area</th>
<th>Dead Clinic loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991–1996</td>
<td>386</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2001</td>
<td>261</td>
<td>92</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>2006</td>
<td>214</td>
<td>34</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 2** Biophysical data of patient cohort attending clinic in 2001 and 2006

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Patient cohort 2001</th>
<th>Patient cohort 2006</th>
<th>Relative % change since 2001</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>9.06 (±14.35)</td>
<td>8.66 (±1.43)</td>
<td>-4.41</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>126.43 (±6.56)</td>
<td>126.13 (±18.97)</td>
<td>-0.24</td>
<td>0.8148</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>73.55 (±15.25)</td>
<td>67.38 (±9.73)</td>
<td>-8.39</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Microalbumin/ Creatinine ratio</td>
<td>5.82 (±21.84)</td>
<td>5.49 (±16.26)</td>
<td>-5.67</td>
<td>0.836</td>
</tr>
<tr>
<td>Creatinine</td>
<td>93.70 (±0.97)</td>
<td>96.24 (±46.20)</td>
<td>2.71</td>
<td>0.0909</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.37 (±11.75)</td>
<td>4.62 (±0.90)</td>
<td>-13.97</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Weight</td>
<td>75.04 (±3.41)</td>
<td>82.31 (±14.79)</td>
<td>9.69</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>BMI</td>
<td>25.32 (±0.27)</td>
<td>27.72 (±5.17)</td>
<td>9.49</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Insulin units/Kg</td>
<td>0.75 (±0.23)</td>
<td>0.79 (±0.28)</td>
<td>5.33</td>
<td>0.597</td>
</tr>
</tbody>
</table>

*Mean values derived from all attendances 1991–2001. **Mean values derived from last attendance 2006.
*Significance taken as P < 0.05.
of medication had also occurred in the 5 years between the two guidelines.

**Medication**

The use of medication to achieve these targets was also reviewed. The guidelines in 2001 were more cautious in addressing cardiovascular risk factors in patients with type 1 diabetes, than perhaps current ones are, with the ADA, Scottish Intercollegiate Network (SIGN) and others now recommending tighter targets.8–11 Most of the patients were on a pre-mixed biphasic regime of insulin administration in 2001, the type of insulin used was not accurately recorded and consequently we were unable to determine whether the newer analogue insulins were being used to any degree at that time. Only small proportions of the clinic population were being treated actively for raised blood pressure, cholesterol or nephropathy (as determined by a raised ACR). This data is shown in Table 4. It is noticeable that an increase in the use of MDI insulin, ACE inhibitors/ARBs, Statins, other blood pressure medication and even Metformin (no patients were using metformin when assessed in 2001) had occurred over the review period.

The results show that in a group of patients followed up in the same clinic for an extended period of time by the same diabetes team, small but statistically significant improvements in the biological measurements of disease can be made. These changes reflect a responsive approach to the management of the risk factors for glycaemic control and cardiovascular disease over more recent years.

**Discussion**

Since the publication of the Diabetes Control and Complications Trial (DCCT) healthcare professionals have strived to improve the glycaemic control of patients with type 1 diabetes. This process has not been easy, as many factors other than insulin use can influence the ability of the patient and the diabetes team to attain the recommended goals.12–14 Recognition of other cardiovascular risk

### Table 3 Proportions of clinic cohort achieving targets in 2001 and 2005

<table>
<thead>
<tr>
<th>Measurement</th>
<th>2001 Target Value</th>
<th>Percentage of clinic at target in 2001 (number of patients)</th>
<th>2005 Target Value</th>
<th>Percentage of clinic at target in 2006 (number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>&lt;7%</td>
<td>3.74% (8)</td>
<td>&lt;6.5%</td>
<td>5.14% (11)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>&lt;130</td>
<td>69.16% (148)</td>
<td>&lt;130</td>
<td>63.62% (134)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>&lt;80</td>
<td>84.58% (181)</td>
<td>&lt;80</td>
<td>93.93% (201)</td>
</tr>
<tr>
<td>Microalbumin/Creatinine ratio (mg/mmol)</td>
<td>&lt;3.5</td>
<td>77.10% (165)</td>
<td>&lt;3.5</td>
<td>83.64% (179)</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>&lt;120</td>
<td>95.79% (205)</td>
<td>&lt;120</td>
<td>93.93% (201)</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/l)</td>
<td>&lt;5.0</td>
<td>37.38% (80)</td>
<td>&lt;4.0</td>
<td>27.10% (58)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>20–25</td>
<td>50.00% (107)</td>
<td>20–25</td>
<td>29.44% (63)</td>
</tr>
</tbody>
</table>

### Table 4 Use and change of insulin and medication by clinic cohort in 2001 and 2006

<table>
<thead>
<tr>
<th>Medication</th>
<th>Percent and (number) of clinic patients in 2001 using medication</th>
<th>Percent and (number) of clinic patients in 2006 using medication</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>62.61% (134)</td>
<td>33.17% (71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Twice daily</td>
<td>33.18% (71)</td>
<td>65.42% (140)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MDI</td>
<td>4.21% (9)</td>
<td>1.40% (3)</td>
<td>0.08</td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
<td>26.16% (56)</td>
<td>45.34% (97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Statin</td>
<td>12.15% (26)</td>
<td>59.81% (128)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other Blood Pressure treatment</td>
<td>7.47% (16)</td>
<td>22.43% (48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metformin</td>
<td>0%</td>
<td>15.89% (34)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values of significance compared using test of significance on two independent proportions. MDI: Multiple dose injection.
factors in the morbidity and mortality of patients with type 1 diabetes has been reflected in the management guidelines produced by leading professional bodies and early intervention and aggressive management policy has been advocated.\textsuperscript{10,15}

It is important to assess if such recommendations are actually attainable in day to day clinical practice. Evidence demonstrates that sub selecting ‘at-risk’ groups within a clinic population and intervening with focused and repeated targeting of the problem areas can improve outcomes in the short term, albeit in patients with type 2 diabetes.\textsuperscript{16} One might expect a comparable approach to be similarly effective in patients with type 1 diabetes.

As effective as short term interventions may be, a sustained improvement in the cardiovascular risk factors is the ultimate goal to improve morbidity and mortality. This cohort, managed in the ‘real-world’ to contemporary standards, show that over a 5-year period small but statistically significant improvements in the biophysical markers can be made. It is clear, however that these improvements are small, and come at no little cost. The relative amounts of medication used by the patients increased significantly over the time period observed. If these improvements can be sustained and built upon, then the benefits to the patients in terms of improved health will be worth this intensive approach.

It is important to ask when outcomes improve, which intervention was responsible although it is difficult to identify the particular intervention which resulted in benefit. For example, glycaemic control is influenced by factors other than prescribed insulin. Patient education and continued communication between healthcare professional and patient, is important. The DARTS-MEMO study\textsuperscript{14} clearly demonstrated that prescriptions for insulin, for patients with type 1 diabetes, are not always completed. It was suggested that up to 28% of the patients in this group had occasions of omission of insulin.

Our cohort had changes in their insulin use and 16% were taking metformin in addition. A shift from the predominant biphasic pre-mixed insulin use to a multiple dose injection (MDI) regime using analogue insulin was one of the more obvious changes that had occurred. Less hypoglycaemia may be experienced with analogue insulin use and the subsequent reduction in fear of hypoglycaemia could then allow a more aggressive dose titration policy and subsequent improvement in glycaemic control \textsuperscript{17} although not all studies supports this.\textsuperscript{18} It is unlikely that a simple change in insulin regime like this could be wholly responsible for improved control. Other evidence suggests no significant change occurs.\textsuperscript{19} It is possible that regular contact with the patients by an experienced team encouraging self management is also responsible for improvements.

Contemporary guidelines for the management of lipids and blood pressure were followed. There were small, but significant improvements in both of these parameters, although there was no significant improvement in systolic blood pressure. The reason for the fall in diastolic pressure but not systolic pressure isn’t entirely clear, but it is a well recognized phenomenon. Lowering diastolic blood pressure however does confer some benefit.\textsuperscript{20}

A significant fall in the total cholesterol over the two sample periods occurred despite no change in the dietary advice issued to these patients. Clearly, use of statin therapy in this population is effective at lowering cholesterol, if a little controversial, with the suggestion that only those with overt nephropathy actually benefit from long term risk reduction.\textsuperscript{21}

Aside from this, improvement in serum lipid profiles is also seen with improving glycaemic control.

This group of patients mean serum creatinine values were unchanged and no deterioration in the mean urinary microalbumin values occurred which may actually reflect blood pressure treatment, given the known associations.\textsuperscript{22}

It is clear however, that a significant increase in the amount of medication is required by the patients to achieve both blood pressure and cholesterol control. The pill-burden of patients with type 2 diabetes has been recognized for some time and is partially a factor in non-compliance with medication use. Patients with type 1 diabetes are now also facing a similar problem as the use of medication to control cardiovascular risk factors is increasing.

The influence of tighter targets for diabetes care over the period reviewed here should be considered. It is difficult to attribute overall improvements in care to a change in practice recommendations. The compliance with guidelines in a clinic setting is variable and often targets are individualized for each patient.\textsuperscript{23} In conclusion, improvements are seen in the proportion of type 1 diabetes patients achieving glycaemic and cardiovascular risk factor targets. Although less achieve the tighter targets set more recently, the proportion achieving the preceding goals have increased significantly.

\textbf{Conflict of interest:} None declared.

\textbf{References}

1. Hornquist JO, Wikby A, Andersson PO, Dufva AM. Insulin-pen treatment, quality of life and metabolic