Glycaemic streaming in type 1 diabetes: implications for intervention?

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Abstract
Evidence exists that mean glycaemia in individuals with type 1 diabetes may remain remarkably constant (glycaemic ‘streaming’ or ‘tracking’). We have re-examined this in a group of type 1 patients, to explore whether any subgroups may be more or less amenable to glycaemic improvement.

We made a retrospective analysis between 2003 and 2007 of 181 people with type 1 diabetes. Basic demographic information, and sequential glycated haemoglobin (HbA1c) levels during the five-year follow-up period (2003–2007), were recorded. First (2003) and last HbA1c levels were recorded, and mean HbA1c for the whole period. These were analysed as a total group, by gender, and by glycaemic control (initial HbA1c over or below 64mmol/mol [8.0%]).

Mean age was 41±8 years, diabetes duration 19±9 years, 58% were male, and mean HbA1c was 75±17mmol/mol (9.0±1.6%). Over the study period there was a small improvement in total population mean HbA1c (75±17 to 72±16mmol/mol [9.0±1.6 to 8.7±1.5%], p=0.003). This was accounted for by improvements in male (74±17 to 70±15mmol/mol [8.9±1.6 to 8.6±1.4%], p=0.005) and poorly-controlled (HbA1c ≥65mmol/mol [8.1%]) patients (79±15 to 75±15mmol/mol [9.4±1.4 to 9.0±1.4%], p=0.002). Female and well-controlled (HbA1c ≤64mmol/mol [8.0%]) patients showed no change in mean glycaemia.

Most patients maintained closely similar HbA1c levels over time. Interventions in type 1 diabetes may be more usefully aimed at risk factors rather than glycaemia. Copyright © 2013 John Wiley & Sons.


Key words
type 1 diabetes; glycaemia control

Introduction
It is common clinical experience that glycaemic streaming in type 1 diabetes tends to remain remarkably stable over time, and that intervention to control often has little or only transient effect. This phenomenon is sometimes known as glycaemic ‘streaming’ or ‘tracking’. There is a very limited supporting literature, but it has been reported from both adult1 and paediatric2 type 1 populations.

Considerable effort and resources are expended on trying to lower HbA1c levels above agreed targets, in order to reduce future complication risk associated with persistent hyperglycaemia.3 We have therefore revisited the issue of glycaemic streaming in a large group of type 1 patients followed for a five-year period. Our aim was to confirm and characterise HbA1c tracking particularly in groups with different levels of long-term glycaemic control; and also to investigate the relationship with insulin regimens and doses, and frequency of clinic attendance.

Patients and methods
The study looked at retrospective data over a five-year period between 2003 and 2007 taken from a database of type 1 patients attending consultant clinics at the Walton Diabetes Centre, Aintree University Hospitals, Liverpool, UK. Patients aged between 25 and 60 years, with diabetes duration between 2 and 40 years were selected for inclusion if they had attended a clinic for a minimum of four appointments between 2003 and 2007. Patients who were not seen in the start or end years of 2003 and 2007 were excluded, as were women who were either pregnant or receiving pre-pregnancy care during this period. In all, 181 patients were finally available for the study. Clinical information was obtained from patient records.

During the study period, all members of the diabetes care team were committed to optimising glycaemic control in people with type 1 diabetes. This included: referral to the diabetes specialist nurse and dietitian; structured individual patient education; movement from two- to four-times daily injection therapy
if indicated; dose adjustment by patients or diabetes specialist nurses; and addition of metformin to insulin in some cases. During the period of study, continuous subcutaneous insulin infusion (CSII, ‘insulin pumps’) was not available to patients, neither was structured dietary carbohydrate counting (such as the ‘DAFNE’ programme). Both of these facilities became available shortly after the study ended.

Demographic data, complication status and attendance. Age, gender, body mass index (BMI), duration of diabetes, HbA1c, insulin doses and frequency of insulin injections were recorded. Other information extracted included the presence of microvascular and macrovascular disease and hospital diabetes clinic attendances.

Glycated haemoglobin (HbA1c). A minimum of four HbA1c measurements over the five-year period were recorded. This included a baseline HbA1c measured in 2005 and a closing measurement in 2007. Additionally, over the five-year period, a mean of all individual HbA1c measurements was calculated (five-year mean). The method of HbA1c assay during the study period was high pressure liquid chromatography (HPLC), and was aligned to the Diabetes Control and Complications Trial.

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 years</th>
<th>5 years</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Total group (n=181)</td>
<td></td>
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<tr>
<td>HbA1c – mmol/mol (%)</td>
<td>75±17 (9.0±1.6)</td>
<td>72±16 (8.7±1.5)</td>
<td>p=0.003</td>
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<tr>
<td>BMI – kg/m²</td>
<td>26.7±4.3</td>
<td>27.5±5.0</td>
<td>p=0.002</td>
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<tr>
<td>Insulin dose – U/kg*</td>
<td>0.76±0.26</td>
<td>0.77±0.38</td>
<td>NS</td>
</tr>
<tr>
<td>Males (n=105)</td>
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<td></td>
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<tr>
<td>HbA1c – mmol/mol (%)</td>
<td>74±17 (8.9±1.6)</td>
<td>70±15 (8.6±1.4)</td>
<td>p=0.005</td>
</tr>
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<td>BMI – kg/m²</td>
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<td>26.8±3.8</td>
<td>p&lt;0.001</td>
</tr>
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<td>Insulin dose – U/kg*</td>
<td>0.75±0.27</td>
<td>0.79±0.37</td>
<td>p=0.34</td>
</tr>
<tr>
<td>Females (n=76)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c – mmol/mol (%)</td>
<td>76±17 (9.1±1.6)</td>
<td>74±17 (8.9±1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI – kg/m²</td>
<td>27.4±4.8</td>
<td>28.2±6.0</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin dose – U/kg*</td>
<td>0.77±0.24</td>
<td>0.73±0.19</td>
<td>p=0.003</td>
</tr>
</tbody>
</table>

Results are mean ± SD. *Data were incomplete for insulin doses in some patients. Figures given are for n=142 at 0 years and n=109 at 5 years. For males n=80 at 0 years, and n=65 at 5 years. For females n=62 at 0 years, and n=44 at 5 years.

Table 2. Changes in HbA1c and BMI levels for the whole group, and by gender, over 5 years of follow up

Statistical analysis. Data were recorded onto a proforma for each patient, and transferred to a Microsoft Office Excel worksheet 97–2003. Student’s paired and unpaired t-tests (or Mann-Whitney U test) as appropriate were used to compare quantitative data. Proportionate data were compared using a Chi-square or Fisher’s exact test. Statistical significance was taken at p<0.05. Statistical analysis was performed using the Statistical Package for Social Sciences (Version 18.0).
The study was approved and registered by the Aintree University Hospital Clinical Standards and Audit Group.

Results

Group characteristics. Table 1 shows the baseline characteristics of the total group of 181 type 1 patients. Mean (±SD) age was 41±8 years and diabetes duration 19±9 years. Fifty-eight percent were male and mean HbA1c was 7.9±3.8% (mean ± SD). When the HbA1c and BMI drifts were analysed by sex, an interesting pattern emerged. The glycaemic improvement (accompanied by a BMI increase) was mostly accounted for by the male sub-population (HbA1c 74 to 70mmol/mol [8.9 to 8.6%], and BMI 26.1 to 26.8). These were both statistically significant, whereas the similar drift in females (HbA1c 76 to 74mmol/mol [9.1 to 8.9%], and BMI 27.4 to 28.2) was not significant. Interestingly, although the males showed glycaemic improvement, their insulin dose did not alter significantly, whereas in the females (with no significant glycaemic change), insulin dose fell significantly.

HbA1c and BMI changes with time. During the five-year study period (2003 to 2007), there was a small but significant fall in mean HbA1c for the whole group (75±17 to 72±16mmol/mol [9.0±1.6 to 8.7±1.5%], p=0.005); see Table 2. This was accompanied by a BMI increase from 26.7±4.3 to 27.5±5.0 (p=0.002). During the observation period there was no significant change in total insulin dose (0.76±0.26 units/kg to 0.77±0.38 units/kg). When the HbA1c and BMI drifts were analysed by sex, an interesting pattern emerged. The glycaemic improvement (accompanied by a BMI increase) was mostly accounted for by the male sub-population (HbA1c 74 to 70mmol/mol [8.9 to 8.6%], and BMI 26.1 to 26.8). These were both statistically significant, whereas the similar drift in females (HbA1c 76 to 74mmol/mol [9.1 to 8.9%], and BMI 27.4 to 28.2) was not significant. Interestingly, although the males showed glycaemic improvement, their insulin dose did not alter significantly, whereas in the females (with no significant glycaemic change), insulin dose fell significantly.

The coefficient of variation of HbA1c was 7.9±3.8% (mean ± SD), with no significant difference between males and females. This value was similar to that found by Jorde and Sundsfjord.1 Overall, 66% of patients stayed within 1% (11mmol/mol) of baseline HbA1c over the five years of follow up. This is in excess of the figure of 50% in the first description of glycaemic ‘streaming’.1

Comparison of patients with ‘acceptable’ and ‘poor’ control. Tables 3 and 4 compare patients with a baseline HbA1c ≤64mmol/mol (8.0%) (Group 1 – ‘acceptable’ control), and those with a baseline HbA1c ≥65mmol/mol (8.1%) (Group 2 – ‘inadequate’ control). In Table 3 it can be seen that there were no significant differences between these patients in terms of age, diabetes duration, and BMI. There was a small but significant difference in gender ratio, with more males in Group 1. Retinopathy and microalbuminuria were significantly more common in Group 2 patients. There was also a trend for other complications to be more common in this group, but this did not reach significance. Over the five years, Group 2 patients were seen more frequently, but missed more clinic appointments than those in Group 1.

Table 4 examines trends over the five years of observation for the two groups. It can be seen that HbA1c remained remarkably static – thus in Group 1 the baseline, five year, and overall mean HbA1c levels were 56mmol/mol (7.3%), 55mmol/mol (7.2%) and 56mmol/mol (7.3%) respectively (not significantly different). BMI increased slightly but significantly, but there was no difference over the five years in insulin dose or number of injections per day.

For Group 2, the HbA1c levels again remained close, though there was a significant drop from 79mmol/mol (9.4%) at baseline to 75mmol/mol (9.0%) at five years, and the overall five-year mean was also slightly significantly different from either figure at 77mmol/mol (9.2%). As with Group 1, there was a small but significant rise in BMI, but no difference over the five years in insulin dose, although there was a significant increase in the number of patients using multiple insulin injections.

Discussion

Our five-year sequential data on glycaemic control in a large number of people with type 1 diabetes took place

<table>
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<tr>
<th>Variable</th>
<th>0 years</th>
<th>5 years</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Group 1 (n=32)</td>
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<tr>
<td>HbA1c – mmol/mol (%)</td>
<td>56±6 (7.3±0.6)</td>
<td>55±9 (7.2±0.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean 5-year HbA1c mmol/mol (%)</td>
<td>–</td>
<td>56±6 (7.3±0.6)</td>
<td>NS (v. 0 and 5 years)</td>
</tr>
<tr>
<td>BMI – kg/m²</td>
<td>26.2±3.2</td>
<td>27.4±3.5</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Insulin dose – U/kg*</td>
<td>0.82±0.33</td>
<td>0.83±0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple insulin injections</td>
<td>18 (56%)</td>
<td>21 (66%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

| Group 2 (n=149) | | | |
| HbA1c – mmol/mol (%) | 79±15 (9.4±1.4) | 75±15 (9.0±1.4) | p=0.002 |
| Mean 5 year HbA1c mmol/mol (%) | – | 77±13 (9.2±1.2) | p=0.03 and p=0.008 (v. 0 and 5 years) |
| BMI – kg/m² | 26.7±4.4 | 27.4±5.2 | p=0.002 |
| Insulin dose – U/kg* | 0.75±0.24 | 0.76±0.25 | NS |
| Multiple insulin injections | 89 (60%) | 113 (76%) | p=0.004 |

Results are mean ± SD. *Data were incomplete for insulin dose in some patients; figures given are for n=28 (Group 1) and n=72 (Group 2). Fisher’s exact test was used to compare the usage of 4 times daily insulin. Definitions of ‘HbA1c ≤64mmol/mol (8.0%)’ and ‘HbA1c ≥65mmol/mol (8.1%)’ are as in Table 3.

Table 4. Five-year changes in HbA1c, BMI, insulin dose and regimen for Group 1 patients (baseline HbA1c ≤64mmol/mol or 8.0%) and for Group 2 patients (baseline HbA1c ≥65mmol/mol or 8.1%)
in an era of accepted commitment to optimised glycaemia. Despite major health care team input, only a slight population improvement in HbA1c occurred (75±17 to 72±16 mmol/mol [9.0±1.6 to 8.7±1.5%], p=0.003), and this reflected improvement among males but not females (Table 2). When comparing well (HbA1c ≤64 mmol/mol [8.0%]) and poorly (HbA1c ≥65 mmol/mol [8.1%]) controlled patients, the well-controlled group had essentially identical control throughout the five-year period of observation. The poorly-controlled group showed a small but significant HbA1c improvement (79±15 to 75±15 mmol/mol [9.4±1.4 to 9.0±1.4%], p=0.002) – see Table 4.

The data suggest that, over time, individual HbA1c levels do remain remarkably ‘streamed’ or ‘tracked’, though small improvements can occur in specific sub-groups – notably males and those with poor baseline control. Interestingly, although improved glycaemia in these sub-groups was associated with small but significant rises in BMI (a well-known phenomenon), there was not a similar rise in mean insulin dose (Tables 2 and 4). Perhaps unsurprisingly, poor control was associated with more non-attendance at clinic visits. Although it is empirically plausible that it may be easier to lower high HbA1c levels, than those already at or near target levels, the gender difference we observed in glycaemic streaming is less easy to explain. However, some studies have suggested that mean glycaemia in female type 1 patients may be higher than male counterparts, and that females (particularly young females) may be more resistant to attempts to intensify insulin treatment. This may relate to under-treatment with insulin among females, sometimes known as ‘insulin omission’ or ‘insulin restriction’ – a phenomenon which may relate to weight control.

As far as we are aware, only four other studies have assessed in detail glycaemic streaming in type 1 diabetes, three of which were in paediatric type 1 populations. In 2000, Jorde and Sundsfjord assessed 372 adult type 1 patients between 1992 and 1997. Although overall glycaemic trends were not assessed, they found a close correlation between first and last HbA1c. Also, major clinical events, such as heart disease and laser treatment for retinopathy, had a small but non-significant lowering effect on HbA1c, but intensification of insulin treatment did not. An interesting finding was that, in recently-diagnosed patients, the mean HbA1c between 3–12 months post-insulin initiation was a strong predictor of the five-year HbA1c.

The second study was by Edge et al. and concerned 362 paediatric type 1 patients (age 0–18 years) observed between 2001 and 2009. A major population improvement in HbA1c was found, as with our study (77±16 to 65±14 mmol/mol [9.2±1.5 to 8.1±1.3%], p<0.0001). However, within this improvement, marked individual ‘tracking’ was found, and poor control at six months post-diagnosis rarely improved in subsequent years. Two further recent paediatric studies have shown that HbA1c at 12 months post-diagnosis was predictive of future control.

Our study is unique in that it involves a large adult population of type 1 patients followed up for five years, and it has identified sub-groups with and without the potential for glycaemic improvement. Our findings and those of others have important implications for the care of patients with type 1 diabetes. Attempts to improve established poor glycaemic control currently consume large amounts of medical and nursing time and resources, but the returns for these efforts are small. It may be that resources should be diverted to potentially more rewarding aspects of type 1 diabetes care – for example, lipid control, optimisation of blood pressure, smoking cessation, and intensive microalbuminuria management.

Intensification of glucose control should perhaps be prioritised to the first 12 months after diagnosis, as the evidence suggests that good control achieved in this period will continue long term.

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We are grateful to all of the staff of the Diabetes Centre, Aintree University Hospital, Liverpool, involved in the care of people with type 1 diabetes.

Declaration of interests
There are no conflicts of interest declared.

References