Glycaemic levels triggering intensification of therapy in type 2 diabetes in the community: the Fremantle Diabetes Study

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ABSTRACT

Objective: To assess the effectiveness of the management of type 2 diabetes in an urban Australian setting.

Design and setting: The Fremantle Diabetes Study (FDS), a community-based longitudinal observational study.

Patients: 531 FDS participants with type 2 diabetes, with mean age, 62.4 years (95% CI, 40.9–79.3 years), 54% male, median diabetes duration 3.0 years (interquartile range [IQR], 0.7–7.0 years), with valid data from the baseline FDS assessment and five subsequent annual reviews between 1993 and 2001.

Main outcome measures: Glycated haemoglobin (HbA_{1c}) levels at annual review visits before and after change in blood glucose-lowering therapy.

Results: Over 2893 patient-years of follow-up, 97 patients (18%) progressed from dietary management to therapy with oral hypoglycaemic agents (OHA), and 45 (9%) progressed from OHA to insulin therapy, after a median duration of diabetes of 4.0 years (IQR, 2.9–5.5 years) and 8.1 years (IQR, 5.5–13.0 years), respectively. Median HbA_{1c} concentrations (IQR) at the review before OHA or insulin were started were 7.7% (6.9%–8.8%) and 9.4% (8.0%–10.7%), respectively. At the next annual review, HbA_{1c} levels in the two groups had fallen to 7.4% (6.5%–8.1%) and 7.9% (7.2%–9.5%), respectively ($P \leq 0.001$). Intensification of therapy was associated with beneficial changes in serum lipid profiles, but not with an increase in frequency of hypoglycaemia.

Conclusions: Most Australian patients with type 2 diabetes may be spending most of the duration of their disease with suboptimal glycaemic control ($HbA_{1c} > 7.0\%$), despite the availability of a range of effective therapies, including insulin.

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For editorial comment, see page 317

There is strong evidence, most notably from the United Kingdom Prospective Diabetes Study (UKPDS),[1,2] that the main goal in treating type 2 diabetes should be to achieve blood glucose levels as close as possible to the non-diabetic range to prevent chronic microvascular and macrovascular complications. This evidence is recognised by key national bodies, such as the Australian Diabetes Society[3] and the American Diabetes Association,[4] which recommend a target glycated haemoglobin (HbA_{1c}) level of < 7.0%. As epidemiological analyses reveal no glycaemic threshold for vascular benefit, more stringent goals (including HbA_{1c} < 6.0%) might be considered if the clinical situation allows.[4] The progressive nature of type 2 diabetes means that patients require periodic intensification of blood glucose-lowering therapy with these goals in mind. For example, projections from UKPDS data indicate that most patients will need insulin therapy to maintain a target HbA_{1c} level of < 7.0% after 9 years of diagnosed type 2 diabetes.[5]

Although ample data describe the temporal relationship between glycaemia and intensification of therapy in protocol-driven intervention studies such as the UKPDS, little is known of real-life management in the community. This is especially true of insulin therapy, which patients and prescribing physicians can be reluctant to consider, even when maximal doses of oral hypoglycaemic agents (OHA) have become ineffective.[6,7]

To provide insight into the effectiveness of diabetes management practices in Australia, we analysed longitudinal data on glycaemic control and diabetes treatment from the community-based Fremantle Diabetes Study (FDS). Our main hypothesis was that the HbA_{1c} level that triggers therapeutic change is well above 7.0%, especially in the case of OHA-treated patients progressing to insulin therapy.

METHODS

Patients

We analysed data from the FDS,[8,9] a longitudinal observational study of a representative sample of patients from an area (population, 120 097) surrounding the port of Fremantle in Western Australia. Recruitment strategies, sample characteristics and details of identified but non-recruited patients have been described previously.[8] The FDS recruited 1294 patients with type 2 diabetes between 1993 and 1996. Annual follow-up assessments continued until 2001. The current analysis included the 531 patients (41% of those recruited) who attended the baseline assessment and five subsequent consecutive annual FDS review visits.

The FDS protocol was approved by the Human Research Ethics Committee, Fremantle Hospital, and all patients gave informed consent to participate.

Data collection

At each FDS visit, demographic and clinical information, including details of diabetes management, was documented. Participants underwent a standard clinical examination, and biochemical tests were done on fasting blood and first-morning urine samples.[8]

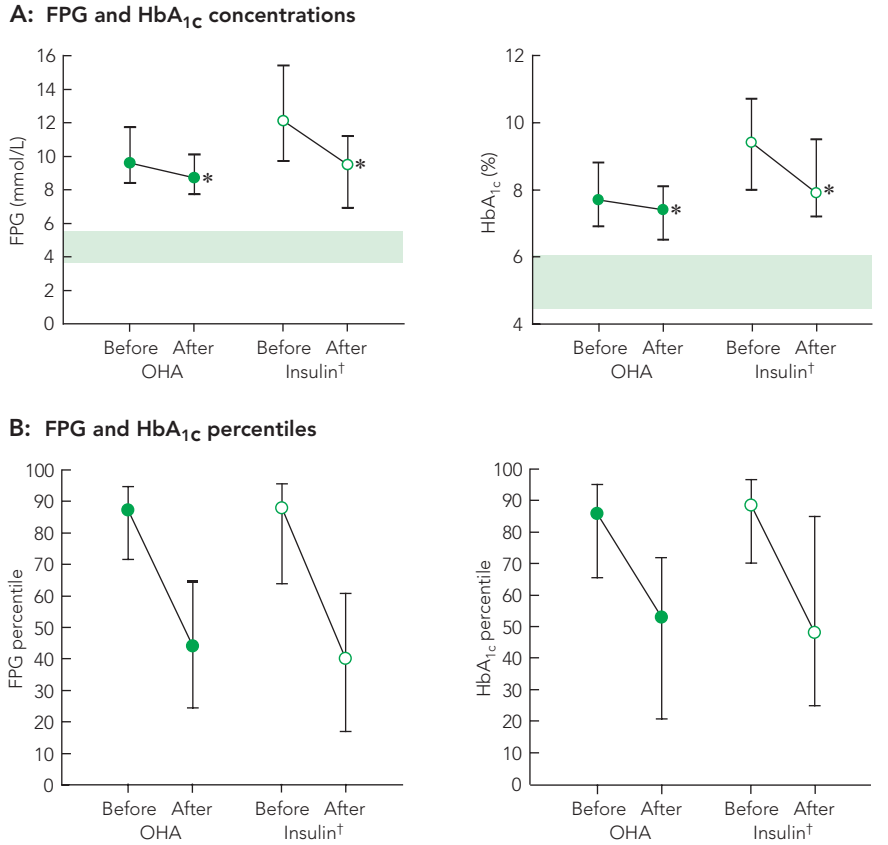
Patients were requested to bring all medications to each visit, and full details of these, including doses, were recorded. Any missing medication data were collected through follow-up telephone calls and/or review of hospital case notes. Compliance with blood glucose-lowering therapy and the number of episodes of symptomatic hypoglycaemia experienced during the previous 12 months were assessed from self-report.

The management of diabetes and other conditions remained with each patient's general practitioner and specialist physician(s) during the course of the study. Details of usual care were also obtained from self-report at each annual FDS assessment.

Statistical analysis

The computer package SPSS for Windows (version 11.5; SPSS Inc, Chicago, Ill, USA) was used for data analysis. Data are presented as proportions, means (95% CI) or, for variables which did not conform to a normal or log-normal distribution, medians (interquartile range [IQR]). Comparison of paired data was by paired *t* test, McNemar's test, and the Wilcoxon signed-rank test. The

1 Fasting plasma glucose (FPG) and glycated haemoglobin (HbA_{1c}) before and after introduction of oral hypoglycaemic agents (OHA) or insulin



Points represent median values, vertical bars are interquartile ranges, and shaded areas are reference ranges.
* There was a significant reduction in levels ($P \leq 0.001$) in each case.
† Insulin introduced instead of or in addition to OHA. ◆

Kruskal–Wallis test was used to compare several independent samples.[10]

To assess whether patients whose therapy was intensified were those most in need, we ranked fasting plasma glucose (FPG) and HbA_{1c} concentration for each patient within their therapy group (non-OHA, OHA or insulin) at each FDS review visit, and converted these ranks to percentiles within the therapy group.

RESULTS

Baseline patient characteristics

At FDS entry, mean age of the 531 patients was 62.4 years (95% CI, 40.9–79.3 years), 54% were male, and median diabetes duration was 3.0 years (IQR, 0.7–7.0 years). Mean body mass index (BMI) was 29.1 kg/m^2 (95% CI, 21.4–40.4 kg/m^2), median FPG level was 8.2 mmol/L (IQR, 6.8–10.4 mmol/L) and median HbA_{1c} level was 7.2% (IQR, 6.3%–8.5%).

Diabetes treatment was diet alone (185; 35%), OHA (metformin and/or sulfonylurea) but not insulin (305; 58%), or insulin with or without OHA (41; 8%).

Compared with the other 763 patients with type 2 diabetes from the baseline FDS cohort, those included in the current analysis were a mean of 2.8 years younger, were more likely to be male (54% versus 45%), and had shorter median diabetes duration (3.0 versus 4.3 years).

Therapeutic progression

During the 2893 patient-years of follow-up, 97 patients (18%) progressed from dietary management to OHA, and 45 patients (9%) progressed from OHA to insulin. Among the latter, 23 (51%) were prescribed insulin in addition to OHA, while the remainder were converted to insulin alone. Assuming that the change in therapy occurred midway between the annual FDS review at which the change was reported and the previous review, OHA was introduced after a median duration of diabetes of 4.0 years (IQR, 2.9–5.5 years) and insulin after a median of 8.1 years (IQR, 5.5–13.0 years).

Effects of therapy change

Median FPG and HbA_{1c} concentrations at the annual FDS visits immediately before and after intensification of therapy are shown in Box 1A, and concomitant changes in BMI, blood pressure and serum lipid levels are summarised in Box 2.

Fasting serum triglyceride levels fell significantly in both those who progressed to OHA and those who progressed to insulin. The former group also had beneficial changes in total serum cholesterol and high density lipoprotein-cholesterol levels, in association with an increase in prescription of lipid-lowering therapy. Those who progressed to insulin had a statistically significant mean 3 mmHg reduction in diastolic blood pressure, despite no change in antihypertensive therapy. BMI and frequency of hypoglycaemia did not change significantly in either group.

Data were available from a further annual FDS review (an average of 18 months after therapy change) in 94 of the 97 patients (97%) who progressed to OHA, and 43 of the 45 (96%) who progressed to insulin. No significant difference in HbA_{1c} level was found between the first visit after the therapy change and the visit a year later in either group; median levels in those who began OHA were 7.4% (IQR, 6.5%–8.1%) at the first visit versus 7.0% (IQR, 6.5%–8.0%) a year later ($P = 0.86$), and in those who began insulin were 7.9% (IQR, 7.1%–9.4%) at the first visit versus 7.9% (IQR, 7.2%–9.4%) a year later ($P = 1.0$).

Nor was there any change in BMI in the group that began OHA, with a mean of 29.8 kg/m^2 (95% CI, 20.3–41.2 kg/m^2) at the first visit after the change versus 29.8 kg/m^2 (95% CI, 20.2–41.8 kg/m^2) a year later ($P = 0.99$). However, in the group that began insulin, BMI increased between these visits, from 29.0 kg/m^2 (95% CI, 21.5–41.0 kg/m^2) to 30.0 kg/m^2 (95% CI, 22.4–41.0 kg/m^2) a year later ($P = 0.004$).

Factors associated with therapy change

There was no relationship between calendar year of assessment and FPG or HbA_{1c} concentrations at the FDS visit immediately before intensification of therapy ($P \geq 0.07$; Kruskal–Wallis test). In addition, there was no consistent pattern in progression rates by

2 Changes in measures of glycaemic control, body mass index, blood pressure and serum lipid levels in Fremantle Diabetes Study patients at annual assessments before and after introduction of oral hypoglycaemic agents or insulin

	Oral hypoglycaemic agents ($n = 97$)			Insulin ($n = 45$)		
	Before	After	*P*	Before	After	*P*
Fasting plasma glucose (mmol/L) (median [IQR])	9.6 (8.4–11.7)	8.7 (7.7–10.1)	< 0.001	12.2 (9.9–15.4)	9.1 (6.8–11.2)	< 0.001
HbA_{1c} (%) (median [IQR])	7.7 (6.9–8.8)	7.4 (6.5–8.1)	0.001	9.4 (8.0–10.7)	7.9 (7.3–9.5)	< 0.001
Body mass index (kg/m^2) (mean [95% CI])	29.8 (21.6–39.4)	29.8 (20.3–41.1)	0.89	29.0 (19.5-48.7)	29.5 (21.5–47.5)	0.10
Hypoglycaemic episodes in past year (median [IQR])	0 (0–0)	0 (0–0)	0.06	0 (0–1.5)	1.0 (0–3.0)	0.11
Systolic blood pressure (mmHg) (mean [95% CI])	146 (107–191)	147 (110–200)	0.62	142 (103–176)	141 (100–219)	0.68
Diastolic blood pressure (mmHg) (mean [95% CI])	77 (48–96)	76 (53–99)	0.46	77 (57–95)	74 (51–101)	0.04
Blood pressure medication (%)	46%	50%	0.61	49%	47%	1.00
Total serum cholesterol (mmol/L) (mean [95% CI])	5.6 (3.9–8.0)	5.3 (3.3–7.4)	0.001	5.7 (3.5–8.4)	5.6 (4.0–9.5)	0.40
Serum HDL-cholesterol (mmol/L) (mean [95% CI])	1.08 (0.63–1.80)	1.12 (0.67–1.77)	0.04	1.05 (0.60–1.89)	1.08 (0.63–1.75)	0.18
Serum triglycerides (mmol/L) (geometric mean [95% CI])	2.1 (0.7–5.9)	1.8 (0.8–5.1)	0.001	2.2 (0.7–9.1)	1.8 (0.8–9.0)	0.008
Lipid-lowering medication (%)	24%	34%	0.02	22%	27%	0.73

HDL = high density lipoprotein. ◆

FDS review number. The percentage of patients who had progressed from diet-based to OHA therapy in the previous 12 months ranged from 10% (at the third review) to 17% (at the fifth review), while the percentage who had progressed from OHA to insulin ranged from 2% (at the third review) to 4% (at the first review).

FPG and HbA_{1c} concentrations of each patient were ranked within their treatment group for each FDS visit and converted to percentiles. For patients changing therapy, FPG and HbA_{1c} percentiles were pooled for each treatment group for the visits before and after the change (Box 1B). The median percentile rank was over 86% for both measures and all treatment groups before therapy change, and dropped to between 40% and 53% after therapy change.

The percentages of patients who reported full compliance with therapy were: for OHA therapy, 83% at the visit after progression to OHA, and 68% at the visit before progression to insulin; and, for insulin, 91% at the visit after insulin was initiated.

Among patients who progressed from diet-based to OHA therapy, 7% reported attending a diabetes outpatient clinic or specialist when this change was made, while 75% were attending a GP for diabetes-related consultations. In the case of patients changing from OHA to insulin (none of whom had already progressed from diet to OHA during the 5-year study period), 40% were attending a diabetes outpatient clinic or specialist at the time, and 86% of these were also under regular GP care for diabetes.

DISCUSSION

These data demonstrate that management of type 2 diabetes in an urban Australian community is not based on proactive intensification of blood glucose-lowering therapy designed to maintain near-normal glucose levels. Most diet-managed patients who began OHA therapy had an HbA_{1c} level over 7.0% at the FDS assessment before this change, while much higher levels of HbA_{1c} were reached in OHA-treated patients before insulin therapy was initiated.

Encouragingly, patients whose FPG and HbA_{1c} levels were among the highest in their treatment groups were those who had their therapy intensified before their next FDS visit, and there was evidence that other vascular risk factors improved in parallel with the HbA_{1c}. However, after an average of 6 months, these patients had become typical of those in their new therapeutic group, with percentile ranks of FPG and HbA_{1c} close to 50%. Thus, although at-risk patients are being identified, glycaemic thresholds for therapeutic action are higher than they should be, and, even when the option of unrestrained insulin therapy is available, suboptimal control persists in most.

It could be argued that glycaemic targets for type 2 diabetes were less ambitious during the first 5 years of our study than later, as the key results of the UKPDS were not released until 1998.[1] However, we found no effect of calendar year on thresholds for therapeutic change in our cohort. Furthermore, the Australian Diabetes Society recommended strict metabolic control ($HbA_{1c} < 7.0\%$) for patients with type 2 diabetes in 1993, after publication of the results of the Diabetes Control and Complications Trial in type 1 diabetes.[3] Indeed, the US National Health and Nutrition Epidemiologic Surveys found a decrease between 1988 and 2000 in the proportion of patients with diabetes achieving an HbA_{1c} level < 7.0%, despite the recommendation for more intensive treatment regimens.[11]

We also found no evidence that feedback on patients' glycaemia from the FDS affected therapy. Although the FDS was not an interventional study, results of annual assessments were sent, with patients' permission, to their GPs and/or specialists. There was no evidence of a pattern in therapy change by FDS visit number, or a higher rate of therapeutic change in the first year after recruitment, which might suggest an effect of this feedback.

As might be expected from the improved glycaemic control in our patients after therapy was intensified, fasting serum triglyceride concentrations fell significantly.[12] We did not observe any change in blood pressure, apart from a mean 3 mmHg reduction in diastolic blood pressure in patients starting insulin, which appeared independent of the effect of antihypertensive therapy.

Insulin initiation has been shown to have variable effects on blood pressure,[13] including benefits, but may also lead to increased blood pressure which accompanies weight gain.[14] Our participants had not gained significant weight by the time of the next FDS visit after intensification of therapy (an average of 6 months later), even after the introduction of insulin. This might indicate a greater readiness to revisit lifestyle modification in our community-based rather than clinic-based participants, but it could also reflect the fact that the levels of glycaemia in our participants did not fall to those associated with a marked reduction in glycosuria. Nevertheless, we found that mean BMI among participants who progressed from OHA to insulin increased significantly after a further year of insulin treatment. This finding is consistent with UKPDS data showing a 2–4 kg body weight increase in the first 1–2 years after randomisation to insulin in intensively-treated patients.[1]

Our data provide some evidence of a link between reduced compliance and therapeutic progression in diabetes, as found in a US study.[13] In our study, the percentage of OHA-treated patients who were fully compliant was greater among those who had just begun OHA (an average of 6 months earlier) than among those who were subsequently started on insulin therapy (the latter having 3–4 years longer duration of diabetes). Those who progressed to insulin therapy had better compliance (over 90%) when it was introduced. However, it is likely that the trend to reduced compliance over time might also occur in this group. Indeed, in a large US study involving a Department of Veterans Affairs regional database of patients using long-term insulin therapy, only 77% adhered to prescribed regimens.[16]

Our data are consistent with the results of shorter-term studies in other contexts. In a primary-care cohort of patients with type 2 diabetes in the UK, identification of HbA_{1c} above the target level of 8.0% led to intensification of therapy in about 50% of cases.[17] In other studies of managed-care patients in the US,[18,19] initiation of new therapies produced a fall in HbA_{1c}, but fewer than 20% of patients had a level below 7.0% during the subsequent 1–2 years. In the UK primary-care study, there appeared to be a particular reluctance to prescribe insulin.[17]

Our data suggest that more Australian patients start insulin therapy under the care of a GP than at the time of attending an outpatient clinic or specialist. The relatively high HbA_{1c} levels in this group suggest that Australian GPs are also reluctant to prescribe insulin, although a range of other factors, such as patient fear of injections, hypoglycaemia and weight gain, and limited availability of specialist and diabetes education services to support insulin initiation, may have contributed. An analysis of these factors was beyond the scope of the present study.

The results of studies from other countries[11,17-19] and our current data provide strong evidence that most patients with type 2 diabetes spend most of the duration of their disease with suboptimal glycaemic control based on the currently recommended HbA_{1c} target of < 7.0%. This is despite the availability of effective therapies, which could be introduced earlier and which, on the basis of the present study, may not increase the risk of hypoglycaemia. Our results indicate that the clear messages of studies such as the UKPDS are not being heeded in Australia.

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COMPETING INTERESTS

None identified.

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