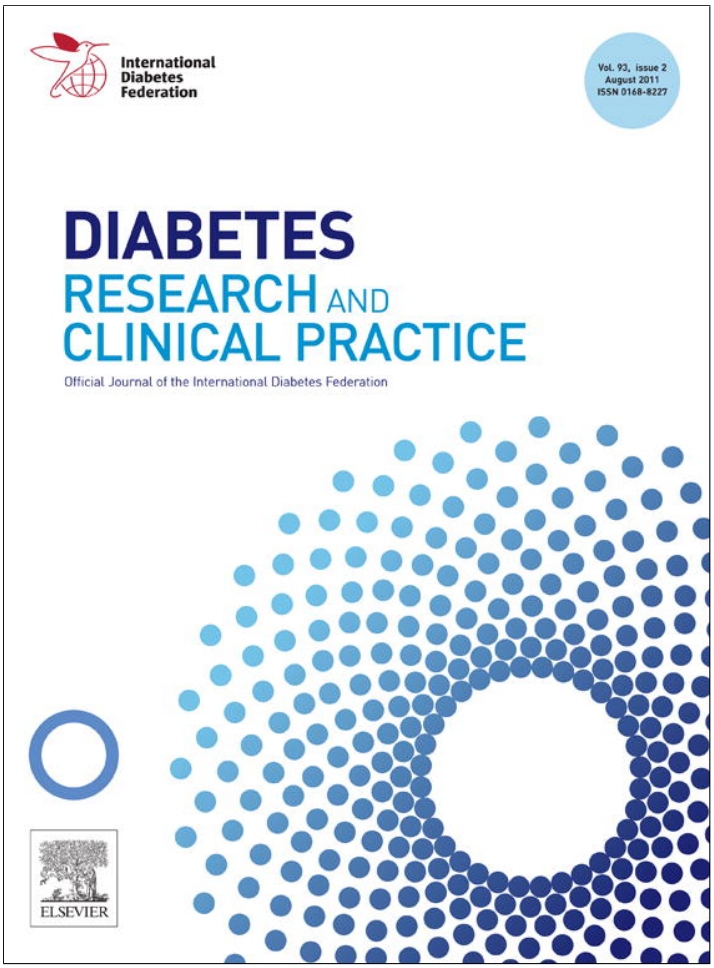

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Brief report

Response at 3 months to insulin dose decisions made at exenatide initiation in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit

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ABSTRACT

It is uncertain what should be done with insulin dose if starting exenatide. In the ABCD nationwide exenatide audit, many patients with type 2 diabetes had worsened glycaemia when insulin was stopped. If starting exenatide, insulin should not be stopped but weaned off only if there is significant glycaemic response.

1. Introduction

Exenatide, a GLP-1 agonist, is not licensed for use in insulin-treated patients with type 2 diabetes [1]. In the Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit, many physicians stopped patients' insulin when starting exenatide to stay within licensing restriction. Some reduced insulin to facilitate weight loss or avoid hypoglycaemia. However, these risked worsening glycaemic control in patients. We examined the effects of insulin dose decisions made at exenatide initiation on treatment response at three months.

2. Subjects and methods

ABCD is a national diabetes specialist society. From December 2008 to December 2009, diabetes physicians across UK submitted anonymised audit data electronically on patients commenced on exenatide therapy. 315 contributors from 126 centres submitted data on 6717 patients. Among other

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[1] On behalf of the ABCD nationwide exenatide contributors (see Appendix A).

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information, data on HbA1c, weight and diabetes treatment changes at exenatide initiation were requested. The audit's general findings have been reported. Overall HbA1c and weight reduction were 0.73% and 5.9 kg while rates of gastrointestinal side effects and hypoglycaemia were 23.7% and 5.6% [2]. In this analysis, HbA1c and weight changes were analysed according to three patient groups at exenatide initiation; non-insulin (Group 1), insulin continued (Group 2), and insulin stopped (Group 3). Patients were excluded if they lacked treatment details or on-treatment (exenatide) three month HbA1c or weight data (taken as ±6 weeks).

Baseline characteristics were compared using appropriate statistical tests. Within and across group HbA1c and weight changes were assessed using paired *t*-tests and ANOVA. ANOVA results with significance of $p < 0.05$ were further examined using Tukey's multiple comparisons for between group differences. Linear correlation compared insulin dose reduction with HbA1c and weight changes. Statistical analyses were performed using Minitab® Release 16.1.

3. Results

3.1. Distribution of patients

6085/6717 patients had baseline diabetes treatment details; 34.2% (2083/6085) were on insulin and 26.2% (546/2083) of these patients stopped insulin. 3673/6085 patients had three month HbA1c and/or weight data; they were divided into Group 1 (non-insulin, 2427 patients), Group 2 (insulin continued, 927 patients) and Group 3 (insulin stopped, 319 patients).

3.2. Baseline patient characteristics and diabetes treatment

Comparisons of baseline characteristics between groups are shown in Table 1. Insulin-treated patients had longer diabetes duration and higher baseline HbA1c. Group 2 had more patients on a basal bolus insulin regimen (37.8% vs 20.9%, $p < 0.001$) and had higher insulin dose requirements (1.1 ± 0.7 U//kg/day vs 0.8 ± 1.2 U/kg/day, $p = 0.009$) than Group 3.

3.3. HbA1c and weight changes at three months

At three months, mean (±SD) HbA1c reduction for Groups 1, 2 and 3 were $0.90 \pm 1.57\%$ ($p < 0.001$), $0.51 \pm 1.51\%$ ($p < 0.001$) and $0.00 \pm 1.91\%$ ($p = 0.968$) (Fig. 1). Weight loss was 4.1 ± 4.6 kg, 4.6 ± 5.0 kg and 6.6 ± 5.2 kg (all $p < 0.001$) (Fig. 2).

Analysis of variance showed significant differences between mean HbA1c reductions between each group (Group 1 > Group 2 > Group 3, all $p < 0.001$ between groups). Similar analysis showed greater weight loss in Group 3 compared with Group 1 and Group 2 (both $p < 0.001$), but were not significant between Groups 2 and 1 ($p > 0.05$). Differences in HbA1c and weight reductions remained significant after adjustment for baseline HbA1c and weight differences among the three groups.

3.4. Effects of insulin dose reduction

Among insulin-treated patients, increasing insulin dose reduction led to less HbA1c reduction ($R = -0.137$, $p < 0.001$) but more weight reduction ($R = 0.209$, $p < 0.001$).

Table 1 – Baseline characteristics of 3673 patients in the audit comparing Groups 1, 2 and 3.

	Group 1 Non-insulin $n = 2427$	Group 2 Insulin continued $n = 927$	Group 3 Insulin stopped $n = 319$	Overall *p*-value
Ethnicity (% Caucasian) ($n = 3286$)	85.3	83.4	88.2	0.143
Gender (% male) ($n = 3514$)	56.4	48.9	58.7	<0.001
Age (years) ($n = 3505$)	54.8 (13.8)	55.1 (10.3)	54.7 (10.7)	0.823
Diabetes duration (years) ($n = 2929$)	8 (5–12)	11 (7–16)	10 (6–15)	<0.001
HbA1c (%) ($n = 3291$)	9.41 (1.67)	9.57 (1.71)	9.67 (1.81)	0.001
Weight (kg) ($n = 3148$)	114.8 (23.3)	113.4 (22.8)	110.7 (21.9)	0.013
BMI (kg/m^2) ($n = 1713$)	40.3 (8.3)	40.2 (7.4)	39.4 (7.2)	0.471
Insulin dose (U/day) ($n = 1052$)	–	120 (87)	91 (111)	<0.001*
Insulin dose (U/kg/day) ($n = 1036$)	–	1.1 (0.7)	0.8 (1.2)	0.009
Diabetes treatment				
No oral therapy	4.7	20.6	11.6	<0.001
1 oral therapy	23.4	55.3	55.5	<0.001
2 oral therapy	46.4	20.4	30.9	<0.001
≥3 oral therapy	25.4	3.6	2.8	<0.001
Basal insulin[a]	–	30.1	42.2	<0.001
Basal bolus insulin[a]	–	37.8	20.9	<0.001
Biphasic insulin[a]	–	30.6	35.4	0.141

Values for continuous variables are expressed as mean (SD) except for duration of diabetes being expressed as median (inter-quartile range).
[a] A small proportion of patients were on other insulin regimens including using rapid/short-acting insulin only, or a combination of biphasic insulin with either rapid/short-acting insulin or long/intermediate-acting insulin.
* Log comparison.

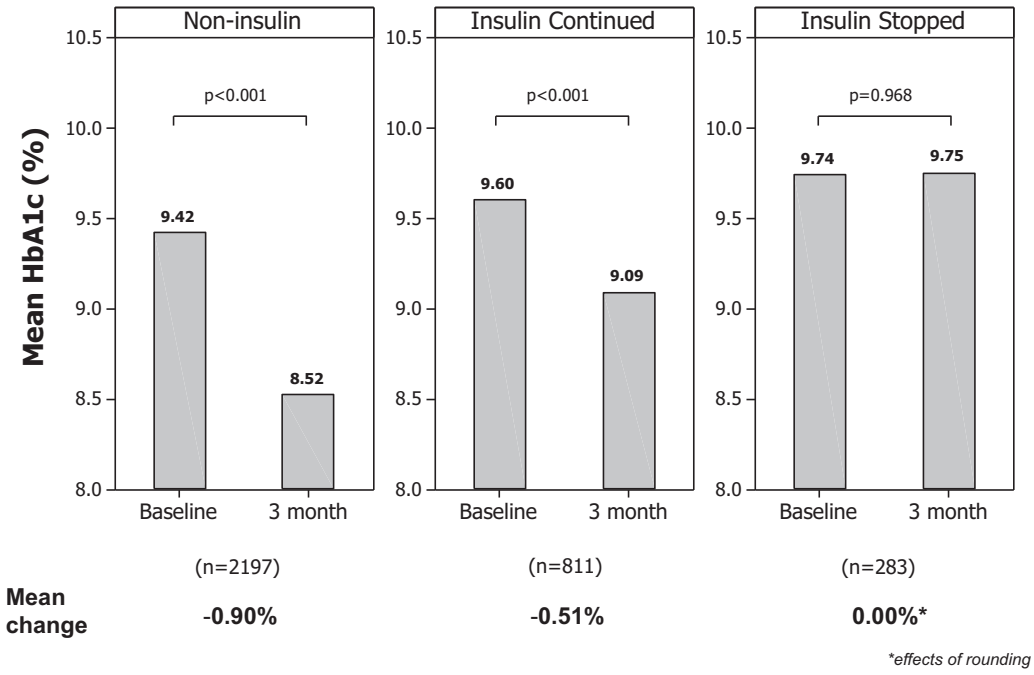

Fig. 1 – Baseline vs 3 month HbA1c with exenatide treatment comparing patient groups.

Patients stopping insulin (mean HbA1c change 0%) had a broad range of HbA1c changes (−7.3% to +5.5%). 48.4% (137/283) of patients had an HbA1c increase including 27.7% with an increase of ≥1%. There were 11 reported cases of ketosis or diabetic ketoacidosis in the audit, seven of these cases occurred in patients who stopped insulin at exenatide initiation. In contrast, rates of hypoglycaemia were lower in patients stopping insulin than those who continued insulin (5.7% vs 9.2%, $p = 0.011$).

4. Discussion

The ABCD nationwide exenatide audit provided useful insights into the starting of exenatide in obese, insulin-treated patients with type 2 diabetes. The audit's size allowed comparisons between insulin and non-insulin patients, as well as an analysis on the effects of reducing or stopping insulin. This contrasts with other retrospective studies

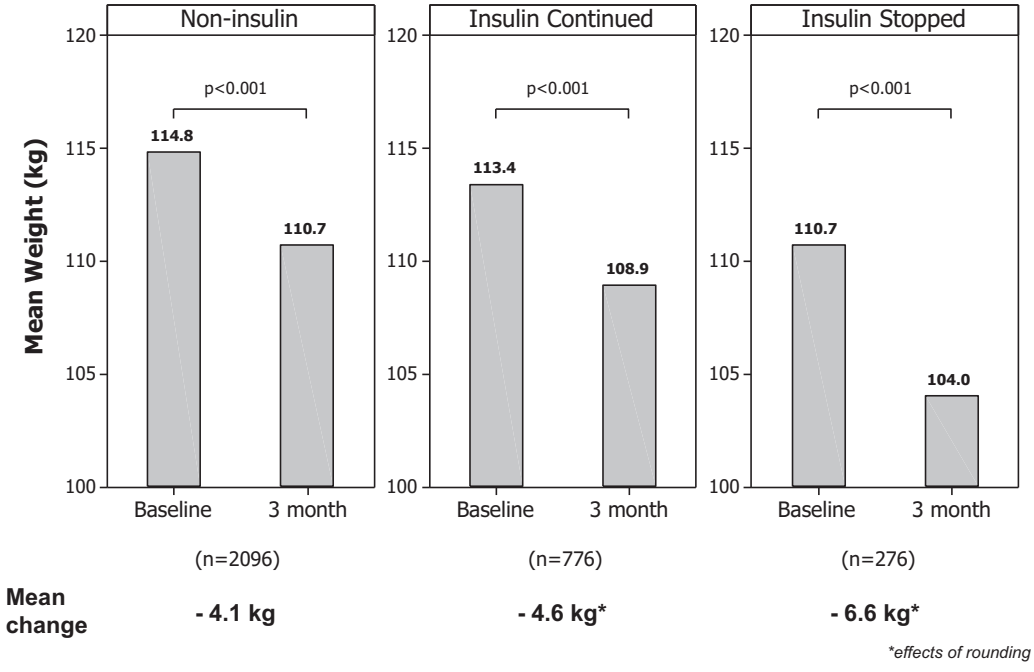

Fig. 2 – Baseline vs 3 month weight with exenatide treatment comparing patient groups.

describing only the effects of adding exenatide in insulin-treated patients [3–5].

Non-insulin patients starting exenatide achieved greater HbA1c reduction and similar weight reduction compared with patients continuing insulin. Weight loss occurred with exenatide even with continued insulin use. Stopping or reducing insulin augmented weight loss at the expense of HbA1c reduction. Nearly half the patients who stopped insulin had worsened glycaemic control.

The mean HbA1c reduction of 0.51% among patients who continued insulin with exenatide was slightly lower than those in two recent randomised trials. Exenatide vs placebo added to basal insulin treatment led to greater HbA1c reduction of 0.6% [6] and 0.69% [7] in these trials, respectively. Patients in the audit were much heavier and more poorly controlled than these trials, as were comparisons with other phase III trials involving exenatide [8]. In a study by Davis et al., patients substituting insulin with exenatide gained a mean HbA1c of 0.3% [9].

This analysis had several limitations. Firstly, there was significant loss of HbA1c and weight data reflecting problems of an audit in real-life clinical practice (missed follow-up, missed measurements or incomplete data entry). This has the potential of introducing bias among available results. Secondly, there was lack of certainty on how quickly insulin dose changes were implemented at exenatide initiation. Insulin could have been completely stopped or weaned off more slowly. If the latter occurred, the full effects on HbA1c and weight may not be evident by three months. Finally, we were unable to determine the degree of insulin optimization in patients in the audit. Hence, we were unable to compare the HbA1c and weight results achieved with exenatide with that of potentially closer titration of the insulin dose.

5. Conclusion

Reducing insulin at exenatide initiation enhanced weight loss but this was at the expense of HbA1c reduction. The glycaemic response of stopping insulin when starting exenatide is heterogeneous; many patients had worsening glycaemic control when insulin was stopped. If starting exenatide in insulin-treated patients, it appears prudent in most patients to continue insulin, and only to wean patients off insulin if there was significant glycaemic response.

Data from this analysis was presented as an oral presentation on September 22, 2010 in the 46th EASD 2010 annual meeting in Stockholm.

Appendix A. List of contributors in the ABCD nationwide exenatide audit

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Conflict of interest

The authors have a competing interest to declare. K.Y.T. is employed as ABCD research fellow, and M.L.C. as data administrator, in the Nationwide ABCD audit programme (which include audits of exenatide and liraglutide) by the Sandwell and West Birmingham Hospitals NHS Trust. These posts are funded by ABCD from grants provided by Eli Lilly Ltd and Novo Nordisk Ltd. K.Y.T. has received educational sponsorship from Eli Lilly, Novo Nordisk, Sanofi-Aventis and Takeda. B.J. has previously received an honorarium from Eli Lilly Ltd. A.B., A.P.M., T.S. and C.W. have no conflict of interests to declare. R.E.J.R. has previously received educational sponsorship, speaker fees and consultancy fees from a number of pharmaceutical companies including Eli Lilly, Novo Nordisk, Sanofi-Aventis, Takeda and GlaxoSmithKline. This audit was independently initiated and performed by ABCD and the authors remained independent in the analysis and the writing of this report.

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