The Effect of Iron and Erythropoietin Treatment on the A1C of Patients With Diabetes and Chronic Kidney Disease

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OBJECTIVE — To examine the effect of intravenous iron and erythropoietin-stimulating agents (ESAs) on glycemic control and A1C of patients with diabetes and chronic kidney disease (CKD).

RESEARCH DESIGN AND METHODS — This was a prospective study of patients with type 2 diabetes and CKD stage IIIB or IV undergoing intravenous iron (group A) and/or ESA (group B). Full blood profiles were determined over the study period. Glycemic control was monitored using A1C, seven-point daily glucose three times weekly, and continuous glucose monitoring (CGM).

RESULTS — There were 15 patients in both group A and group B. Mean A1C (95% CI) values fell in both groups (7.40% [6.60–8.19] to 6.96% [6.27–7.25], $P < 0.01$, with intravenous iron and 7.31% [6.42–8.54] to 6.63% [6.03–7.36], $P = 0.013$, ESA). There was no change in mean blood glucose in group A (9.55 mmol/l [8.20–10.90] vs. 9.71 mmol/l [8.29–11.13], $P = 0.07$) and in group B (8.72 mmol/l [7.31–10.12] vs. 8.78 mmol/l [7.47–9.99], $P = 0.61$) over the study period. Hemoglobin and hematocrit values significantly increased following both treatments. There was no linear relationship found between the change in A1C values and the rise of hemoglobin following either treatment.

CONCLUSIONS — Both iron and ESA cause a significant fall in A1C values without a change to glycemic control in patients with diabetes and CKD. At the present time, regular capillary glucose measurements and the concurrent use of CGM remain the best alternative measurements of glycemic control in this patient group.

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A1C is the most widely accepted and used method of assessing chronic glycemia in patients with diabetes. It is formed by the irreversible binding of glucose to hemoglobin over the lifespan of the erythrocyte (1,2).

Patients with chronic kidney disease (CKD) are commonly anemic due to a variety of reasons, including functional or absolute iron deficiency and erythropoietin insufficiency (3,4). Treatment of anemia in patients with CKD using iron replacement therapy and erythropoietin-stimulating agents (ESAs) has resulted in significant improvements to quality of life and the correction of anemia without the need for blood transfusions (3–5).

There are several studies (6–9) that show a fall of A1C in patients treated with ESA and iron therapy. These studies are mostly in patients already receiving hemodialysis and those without diabetes. The effect of the lowering of the A1C values following either treatment has been postulated to be secondary to the formation of new erythrocytes in the blood stream, causing a change of proportion of young to old cells, and also from an alteration in the red-cell glycation rates (10,11).

Despite this, a comprehensive analysis of the relationship between glycemic control and A1C changes in patients undergoing both iron and ESA therapy has never been performed using robust methods, such as seven-point daily capillary glucose monitoring (7PGM) or using CGM devices. Thus, any class effect that iron therapy and ESA may have on A1C values could in fact represent a parallel change to glycemic control along with the currently postulated physiological changes. Furthermore, the effect of the fall in A1C following these two therapies has not been well studied in patients not already on hemodialysis.

This study therefore sought to establish how intravenous iron and ESA therapy influence A1C values in patients with type 2 diabetes and CKD not on hemodialysis. Robust monitoring of blood glucose was performed throughout the study period to determine if the anticipated fall in A1C was a true reflection of glycemic control.

RESEARCH DESIGN AND METHODS

— This was a prospective study of patients with type 2 diabetes and CKD stage IIIB or IV (estimated glomerular filtration rate [Modification of Diet in Renal Disease] 15–44 ml/min per 1.73 m^2) selected for treatment with intravenous iron and/or ESAs between January 2009 and December 2009 inclusive. All patients were attending a single renal service where the decision to commence iron and ESA therapy was made by the attending physician.

The study consisted of two groups. The first group (group A) were patients selected for iron therapy according to clinical need, and the second group (group B) consisted of patients who were those needing ESA treatment. Glycemic control in both patient groups was assessed in the month leading up to treatment and once again for a 4-week period 4 months after therapy. These assessments comprised the measurement of A1C, seven-point glucose day profiling (7PGM) three times weekly, and CGM for

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a minimum of 48 h. A more detailed account of the study methodology and patients are described below.

Patient selection and exclusion criteria

Iron therapy group (group A). All patients selected for iron therapy had either absolute or functional iron deficiency as evidenced by serum ferritin values <200 μg/l. All patients had hemoglobin ≤10.5 g/dl. Patients in this group were not on previous or concurrent ESA therapy and were vitamin B12 and folate replete. Intravenous iron was given as a single dose in the form of low–molecular weight iron dextran (Cosmofer) dependent on the patient's body weight. This was delivered as an initial intravenous test infusion of 100 mg of iron over 1 h followed by the remaining dose over the next 2–4 h.

ESA therapy group (group B). All patients receiving ESA therapy had hemoglobin ≤10.5 g/dl and were considered iron, vitamin B12, and folate replete prior to initiation. Patients were considered iron replete following a serum ferritin value >200 μg/l or having received intravenous iron at least 6 weeks prior to ESA therapy. ESA treatment was given in the form of darbepoetin α at 750 nano grams/kg fortnightly and continued throughout the period of the study. The dose of ESA was titrated monthly to achieve a target hemoglobin 10.5–12 g/dl.

Exclusion criterion

Patients with known hemoglobinopathy, with a history of transfusion or bleeding with the last 6 months, who had been previously treated with ESA on renal replacement, or with previous transplantation were excluded from the study.

Sample analysis and monitoring of glycemic control

Patients in groups A and B were provided with the Abbott Freestyle Freedom Lite glucose sensor (Abbott Diagnostics, Maidenhead, U.K.). Patients were requested to perform 7PGM three times weekly 1 month before commencement of treatment until the end of the study. 7PGM was defined as premeal, 90-min postmeal, and prebedtime capillary glucose measurements.

CGM was performed using the Medtronic CGMS Ipro Continuous Glucose Recorder (Medtronic Minimed, Northridge, CA). Using this system, measurements of interstitial glucose levels were made 228 times over a 24-h period. Callibration of CGM readings were made based on patient 7PGM over the similar time period. All patients had CGM performed for 2–4 days. This was done prior to ESA and iron therapy and once again at the end of the study.

Results from the 7PGM and CGM were downloaded from their respective meters for data analysis. Results from the CGM included at least a successful 24-h profile over the monitoring period with no gaps >120 mins. The management of diabetes control was left to the patients and their health care professional. Treatment for glycemic control was monitored throughout the study period.

Blood was drawn fasting from all patients for A1C and full blood profile. All A1C measurements were made using ion-exchange chromatography via the Menarini HA-8160 A1C analyser (A. Menarini, Berkshire, U.K.). It has been shown that there is no interference between carbamylated hemoglobin (present in uremia) and A1C using this analyser (12). Patients in groups A and B had samples taken 1 month before commencement of therapy and once again 4 months following treatment initiation.

Data analysis

All data were tabulated using Microsoft Excel and statistical analysis was made using SPSS 16.0 using paired *t* tests where appropriate.

Mean blood glucose (MBG) pre- and posttreatment was calculated by taking the average of the daily mean glucose values where there were three more capillary glucose readings per day. As glucose values were measured more frequently over CGM periods, the results were weighted to ensure each measurement was proportional to the inverse of the total number of measurements taken the same day similar to that done in the A1C-Derived Average Glucose Study (13).

Power calculation

Data from previous studies were used to calculate the statistical power required in the knowledge that iron has previously been shown to have a larger effect on A1C than ESAs (6,14). Assuming the intra-subject variation of A1C is Gaussian (15), nine patients were required to detect a 1.2% fall in A1C in group A and 13 patients to detect a 1.0% fall in group B, with 80% power to an α of $P < 0.05$ using nQuery (Statistical Solutions, Cork, Ireland). Ethical approval was obtained from the local ethics committee prior to the commencement of the study (local research ethics committee [LREC] no. 08/H1304/114).

RESULTS

Patient data

Intravenous iron therapy (group A). Fifteen patients (9 male, six female, all Caucasian, median age 72 years [interquartile range {IQR} 68–74], median albumin-to-creatinine ratio 6.3 [4.3–76.3]) agreed to participated in this arm of the study. Six patients were diet controlled, and nine patients were insulin requiring. The follow-up period was (means ± SD) 16.4 ± 3.7 weeks.

ESA therapy (group B). Fifteen patients (11 male, four female, all Caucasian, median age 70 years [IQR 62–75], median albumin-to-creatinine ratio 9.3 [IQR 6.0–93.4]) were recruited in this group. Four patients were diet controlled, four were on oral hypoglycemic agents, and seven were insulin requiring. The follow-up time in this group was 17.3 ± 3.3 weeks. No patients received additional oral or intravenous iron therapy over the period of the study following the initiation of ESA treatment.

Glucose measurements and control

No new treatments affecting glycemic control (e.g., oral hypoglycemic agents, steroids, ß-blockers) were initiated or altered over the study period in all patients.

The CGM and the 7PGM data included ~1,300 and 250 measurements per subject, respectively, for a total of ~1,500 glucose tests over the entire study period. Using the 7PGM results, there are a mean 4.7 readings a day, of which 31% of the seven-point profiles were complete. The median days of CGM were 6. The results of the CGM were retrospectively calibrated with the 7PGM readings performed over the similar period. MBG in both groups did not change over the study period. The results of these are summarized in Tables 1 and 2.

A1C values

Despite a lack of change of glycemic control in the both groups, A1C concentrations fell significantly ($P < 0.001$ and 0.013, respectively, for groups A and B). There was no linear relationship between the change in A1C and hemoglobin concentration values. (group A, Pearson two tailed, $R^2 = -0.329$, $P = 0.23$; group B, $R^2 = -0.313$, $P = 0.25$).

Table 1—*Patients on iron therapy*

	Before iron mean (95% CI)	After iron mean (95% CI)	*P**
A1C (%)	7.40 (6.60–8.19)	6.96 (6.27–7.25)	<0.001
Hb (g/dl)	9.71 (9.32–10.05)	10.46 (9.97–10.75)	0.001
Hct	0.302 (0.285–0.316)	0.334 (0.314–0.354)	0.007
Ferritin (μg/l)	122 (67–176)	307 (211–403)	<0.001
MBG (mmol/l)	9.55 (8.20–10.90)	9.71 (8.29–11.13)	0.071
Estimated glomerular filtration rate	34.0 (31.9–36.2)	32.8 (30.4–35.2)	0.137

*Paired *t* test.

Subgroup analysis of group B

In the group of patients receiving ESA therapy, there were seven patients (5 male, two female, median age 72 years [IQR 62–79]) who received ESA therapy after iron treatment and eight patients (six male and two female, median age 69 years [61–74]) who received ESA only. All patients who also received iron were treated at least 6 weeks prior to ESA therapy initiation.

There appeared to be a nonsignificant trend toward ESA leading to a further decrease in A1C following the initial fall due to iron (mean A1C 7.3–6.9%, $P = 0.36$ following iron and 6.9–6.7%, $P = 0.13$ following ESA). In contrast, the group of patients receiving ESA therapy without iron had a significant fall in A1C from 7.3 to 6.5% ($P = 0.02$).

MBG did not change in either group (9.12 vs. 9.21 mmol/l, $P = 0.47$ for ESA and iron vs. 8,21 vs. 8.26 mmol/l, $P = 0.71$ for ESA only), and there was a concurrent rise to hemoglobin (9.6–11.76 g/dl, $P < 0.01$ vs. 9.4–11.3 g/dl, $P < 0.01$) and hematocrit (0.310–0.347, $P < 0.01$ vs. 0.331–0.384) values following therapy.

CONCLUSIONS — ESAs and intravenous iron are commonly used therapies in the management of anemia in patients with CKD. Patients with both diabetes and CKD have a higher prevalence of severe anemia compared with patients with CKD alone (16–18). Despite the increased usage of ESA agents, recent findings have shown that the correction of anemia to levels of hemoglobin in excess of 12.5 g/dl in patients with type 2 diabetes using this therapy has not led to an improvement in mortality but rather an increased risk of stroke. This needs to be interpreted carefully, as the two groups received disproportionate amounts of intravenous iron. Indeed, in the placebo group it was noted that there was in increase in the hemoglobin levels with ESA agents. Hence, best practice would suggest that correction of functional and absolute iron deficiency should be obtained prior to commencement of ESA (19). This is the first study to robustly show that iron and ESA treatments result in a fall in A1C, which is independent of glycemic changes in patients with diabetes and CKD stage IIIb and IV.

Discordantly high A1C values compared with glucose readings have been reported in previous studies and case reports on nondiabetic patients with iron deficiency (10,11,20,21) and in patients with type 1 diabetes in childhood and pregnancy (22). The correction of the iron deficiency in all these patient groups has lead to a fall in A1C values in these patients, though the monitoring of glycemic control of patients has not been as robust compared with our study (using methods such as fasting plasma glucose or two premeal readings a day).

Table 2—*Patients on ESA*

	Before ESA mean (95% CI)	After ESA mean (95% CI)	*P**
A1C (%)	7.31 (6.42–8.54)	6.63 (6.03–7.36)	0.013
Hb (g/dl)	9.52 (9.18–9.86)	11.51 (11.15–11.85)	<0.001
Hct	0.324 (0.296–0.350)	0.378 (0.341–0.398)	<0.001
Ferritin (μg/l)	344 (241–447)	332 (211–354)	0.37
MBG (mmol/l)	8.72 (7.31–10.12)	8.78 (7.47–9.99)	0.893
Estimated glomerular filtration rate	30.5 (28.6–33.4)	31.0 (27.3–33.8)	0.613

*Paired *t* test.

Several studies have also shown a fall in A1C concentrations following ESA treatment in patients with diabetes undergoing hemodialysis (7,8). Other than a single case report (23), there was scarce data to support the class effect of this therapy on patients not on hemodialysis.

Nakao et al. (7) reported a fall in A1C in nondiabetic patients with CKD on hemodialysis following ESA therapy. The 1.2% fall in their study was much larger when compared with our results. A plausible explanation is that in contrast to our study, iron therapy was given concurrently, which has likely to have potentiated the A1C-lowering effect reported. A proportion of patients in our study had both therapies, and though there was a similar trend of combined lowering of A1C in this group, this failed to reach statistical significance.

Good glycemic control in patients with diabetes and CKD has been shown to be associated with better survival rates (24). Proper assessment of glycemic control is therefore vital if this is to be achieved. The results of our study show both statistically and clinically significant falls in the A1C following iron and ESA treatment (mean 0.4% following iron and 0.7% following ESA) in the absence of a change in glycemic control.

From a practical view, the data from this study highlights several issues to which diabetes management can be improved in patients with diabetes and CKD. It shows that A1C can be unreliable and can fall following treatment with both iron and ESA therapy. It is essential that health care professionals are aware of the potential fluctuations of A1C that can occur in this patient group. Alternative methods for measuring glycemic control such as capillary glucose testing and CGM should be used, and therapy should not be based on the A1C value alone. This has particular significance when considering national, international, or health service glycemic targets, such as the Quality and Outcome Framework in the U.K., which almost exclusively uses A1C as the sole index by which treatment success is judged.

Glycated albumin has been suggested as an alternative marker to represent glycemic control, as it was noted to be similar (in contrast to A1C, which was higher) in patients with iron deficiency and pre-ESA compared with patients posttherapy (8,20). Though this may be true, further study is still required and better correlation between glycated albumin and glyce-

mic control is still needed before this measurement to be more widely used.

The strengths of this study lies in the robust monitoring of glycemic control in patients. 7PGM and CGMS were used in all patients and glycemic control, treatment, and A1C values were monitored closely. However, this study is limited by its relatively small numbers, and though it managed to show that A1C values fell both with iron and ESA, there were insufficient numbers to confirm whether the combined effect of both therapies had an added A1C-lowering effects compared with a single agent given alone.

Intravenous iron and ESA are increasingly common therapies used in the management of anemia in patients with CKD and diabetes. The present study has been able to confirm that reported changes in A1C following these treatments are indeed independent of changes in glycemic control; therefore, caution is warranted in the interpretation of A1C and management of glycemia when based on this measurement alone. At a time when self-monitoring of blood glucose is being discouraged, especially in non–insulin-treated patients (25), regular capillary glucose measurements, and the concurrent use of CGM if available, seems essential in order to accurately assess glycemic control in this group of patients.

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J.M.N. was involved in the study design, researched and analyzed the data, and wrote the draft manuscript. He also works in the Michael White Research Center and is employed by the Hull York Medical School, Hull. M.C. was responsible for research and discussion of study results. S.B. was also involved in assisting with the study concept and in the discussion of study results and reviewed the final manuscript. They both work in the Renal Department in Hull Royal Infirmary, Hull, U.K., and are employed by the Hull and East Yorkshire National Health Service Trust. E.S.K. and S.L.A. were involved in designing the study. They reviewed the data, rewrote the manuscript, and contributed to the discussion. E.S.K. works in the Department of Clinical Biochemistry and is employed by the Hull and East Yorkshire National Health Service Trust. S.L.A. works in the Michael White Research Centre and is employed by the Hull York Medical School.

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