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Research: Care Delivery

Utility of HbA_{1c} assessment in people with diabetes awaiting liver transplantation

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Abstract

Aims To investigate the relationship between HbA_{1c} and glucose in people with co-existing liver disease and diabetes awaiting transplant, and in those with diabetes but no liver disease.

Methods HbA_{1c} and random plasma glucose data were collected for 125 people with diabetes without liver disease and for 29 people awaiting liver transplant with diabetes and cirrhosis. Cirrhosis was caused by non-alcoholic fatty liver disease, hepatitis C, alcoholic liver disease, hereditary haemochromatosis, polycystic liver/kidneys, cryptogenic/non-cirrhotic portal hypertension and α-1-antitrypsin-related disease.

Results The median (interquartile range) age of the diabetes with cirrhosis group was 55 (49–63) years compared to 60 (50–71) years (P=0.13) in the group without cirrhosis. In the diabetes with cirrhosis group there were 21 men (72%) compared with 86 men (69%) in the group with diabetes and no cirrhosis (P=0.82). Of the group with diabetes and cirrhosis, 27 people (93%) were of white European ethnicity, two (7%) were South Asian and none was of Afro-Caribbean/other ethnicity compared with 94 (75%), 16 (13%), 10 (8%)/5 (4%), respectively, in the group with diabetes and no cirrhosis (P=0.20). Median (interquartile range) HbA_{1c} was 41 (32–56) mmol/mol [5.9 (5.1–7.3)%] vs 61 (52–70) mmol/mol [7.7 (6.9–8.6)%] (P<0.001), respectively, in the diabetes with cirrhosis group vs the diabetes without cirrhosis group. The glucose concentrations were 8.4 (7.0–11.2) mmol/l vs 7.3 (5.2–11.5) mmol/l (P=0.17). HbA_{1c} was depressed by 20 mmol/mol (1.8%; P<0.001) in 28 participants with cirrhosis but elevated by 28 mmol/mol (2.6%) in the participant with α-1-antitrypsin disorder. Those with cirrhosis and depressed HbA_{1c} had fewer larger erythrocytes, and higher red cell distribution width and reticulocyte count. This was reflected in the positive association of glucose with mean cell volume (r=0.39) and haemoglobin level (r=0.49) and the negative association for HbA_{1c} (r=–0.28 and r=–0.26, respectively) in the diabetes group with cirrhosis.

Conclusion HbA_{1c} is not an appropriate test for blood glucose in people with cirrhosis and diabetes awaiting transplant as it reflects altered erythrocyte presentation.

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Introduction

Diabetes is a leading cause of liver disease, with cirrhosis responsible for a considerable number of deaths in people with diabetes in the USA [1]. The association is mediated by multiple mechanisms including dyslipidaemia and altered hepatic fatty acid processing [2]. Peripheral insulin resistance may contribute to the development of diabetes in people with hepatitis

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What's new?

- HbA_{1c} may not be an accurate reflection of blood glucose for the diagnosis/monitoring of diabetes in people with other illnesses or on certain drugs; people with diabetes and liver disease awaiting transplantation are one such group.
- HbA_{1c} was found to be depressed relative to random plasma glucose by 20 mmol/mol in people with diabetes and cirrhosis (n = 28) compared to people with diabetes but no liver disease (n = 125); however, HbA_{1c} was elevated in one person with cirrhosis attributable to α-1-antitrypsin disorder.
- Compromised HbA_{1c} may be related to haematological differences associated with liver disease involving erythrocyte half-life, with shorter/longer times giving less/more opportunity for glycation of haemoglobin.

C [3] and cirrhosis [4]. Post-transplant diabetes is well recognized, with HbA_{1c} testing not being appropriate immediately afterwards as a result of post-transplant anaemia [5] and also rendered inaccurate by some drugs such as ribavirin which is used for hepatitis C treatment [6].

In 2011, the WHO introduced HbA_{1c} assessment for the diagnosis of diabetes mellitus [7]. HbA_{1c} is now widely used for this purpose in primary care, resulting in a doubling of the number of HbA_{1c} assessments requested, and a corresponding decrease in glucose measurement [8]. Since 2014, the use of HbA_{1c} testing has been included in the American Diabetes Association guidelines for the diagnosis of diabetes in hospital [9]. This recommendation has been confirmed by assessment of undiagnosed diabetes in white European people admitted to an Irish hospital [10]. However, whilst the WHO bulletin lists medical conditions and drugs that may affect HbA_{1c}, it provides no references to quantitative evidence [7].

Our hospital laboratory has reviewed HbA_{1c} test results, referring values below the reference range or very high values in people without a previous diagnosis of diabetes for urgent medical attention [8,11]. Evidence is accumulating that various co-existing conditions affect HbA_{1c} and result in misdiagnosis or mismanagement of diabetes [12]. Recently, HbA_{1c} was measured in 200 people with decompensated cirrhosis referred for liver transplantation. Measured HbA_{1c} values were significantly lower when compared with HbA_{1c} calculated from three previous glucose values [13].

Given these concerns, we investigated random plasma glucose and HbA_{1c} in people recruited for research into the relationships between glycaemic markers when attending diabetes clinics at the hospital, and in people with co-existing cirrhosis and diabetes awaiting liver transplant who had available data on glycaemic markers and Model for End Stage Liver Disease (MELD) scores [14].

Participants and methods

Ethics

The West Midlands Local Research Ethics Committee confirmed ethical approval for the Glucose Fructosamine and HbA_{1c} research study investigating the relationships between glycaemic markers in people attending the diabetes clinic at University Hospitals Birmingham NHS Foundation Trust. This study met the requirements of the current revision of the Declaration of Helsinki.

For people with diabetes attending liver clinics between June and September 2012, data were obtained from the electronic patient record for a registered, internal clinical audit (CAB-05641-13) at University Hospitals Birmingham NHS Foundation Trust.

Study cohort

The people with diabetes without liver cirrhosis included adults with no variant haemoglobin (n=125) who were recruited from the diabetes clinic at Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, UK, between June 2007 and June 2009.

The people with co-existing liver cirrhosis and diabetes comprised people from different parts of the UK with cirrhosis of the liver and diabetes, attending day clinics in the Liver Department at Queen Elizabeth Hospital Birmingham, UK, who were being considered for liver transplantation. Those attending between October 2008 and June 2012 were included in the clinical audit; in total, 240 people were reviewed. HbA_{1c} and random plasma glucose measurements, performed at Queen Elizabeth Hospital Birmingham laboratories, were available for 29 out of the 50 transplant candidates with both cirrhosis and diabetes. No other measure of glycaemic control was available to the study. Indications for transplant included one or more of the following complications of cirrhosis: spontaneous bacterial peritonitis; ascites; variceal bleed; and hepatic encephalopathy. Of the 29 participants in this cohort, 15 (52%) had non-alcoholic fatty liver disease, six (21%) had hepatitis C, three (10%) had alcoholic liver disease, two (7%) had hereditary haemochromatosis, one (3%) had polycystic liver and kidneys, one (3%) had α-1-antitrypsin-related liver disease and one (3%) had cryptogenic/non cirrhotic portal hypertension. Data were collected for this preliminary, clinical audit from the Birmingham Systems Prescribing Information and Communications System and the CDS Telepath Systems Ltd databases.

Measurements

All measurements were performed at University Hospitals Birmingham NHS Foundation Trust, with single measurements of HbA_{1c}, random plasma glucose, serum bilirubin and creatinine, and full blood count. Blood was collected

into fluoride oxalate vacutainers for glucose measurement. Biochemical variables were measured on Roche c8000 analysers (Roche Diagnostics Ltd, Burgess Hill, UK) and full blood count on Beckman DxH800 analysers (Beckman Coulter Ltd, High Wycombe, UK).

HbA$_{1c}$ was measured in EDTA blood using an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) aligned TOSOH G8 ion exchange high performance liquid chromatography analysers (Tosoh, Reading, UK) before realignment of their calibrator downwards by the manufacturer in September 2013 [15]. People with abnormal haemoglobin were excluded because HbA$_{1c}$ is not reported by the laboratory in its presence, as were people with a total chromatogram area <500 as specified in the manufacturer's protocol for HbA$_{1c}$ measurement (~80g/l haemoglobin).

The MELD score was calculated using the formula: [0.957 × ln(serum creatinine) + 0.378 × ln(serum bilirubin) + 1.120 × ln(INR) + 0.643] × 10, with creatinine set to 4.06 for participants on haemodialysis [14]. The normal range for the MELD score is 0 to 6, with a score of 40 defined as gravely ill.

Statistical analysis

Data on participants without liver disease were entered into an Excel spreadsheet with robust quality assurance. Biochemical and haematological data were downloaded directly from the laboratory Telepath database. Clinical audit data for participants with diabetes and liver disease were accessed in the electronic patient record and entered into a pre-prepared Excel spreadsheet. Data were analysed with Microsoft Excel, Analyse-it Version 2.22 (Analyse-it Software Ltd, Leeds, UK), SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA) and R version 3.4.0 [16].

The characteristics of the study cohort are presented in Table 1 as median and interquartile range (IQR), count or percentage, with Mann–Whitney or Fisher's exact tests used to compare the groups. Reference ranges were obtained from the hospital laboratory. Simple linear regression was used to assess the relationships between HbA$_{1c}$ and random plasma glucose, with Fig. 1 showing regression lines for both groups and 2SD lines for people with diabetes without cirrhosis. Residual analysis was performed to assess the fit of the model for the regression of HbA$_{1c}$ vs glucose. Some skewness in the HbA$_{1c}$ data was demonstrated in a Normal Q-Q plot of residuals, but there was no evidence of non-linearity. Log transformation of HbA$_{1c}$ values reduced the skewness, but did not affect the linearity, and yielded an R^2 value of 0.44 rather than 0.42. As both models are valid and give similar results, and given the ease of use of non-transformed data, we have not used the log transformation. This has the added advantage that the model is not dependent on the choice of units for HbA$_{1c}$.

Calculation of the difference in the HbA$_{1c}$ intercepts for the people with co-existing liver cirrhosis and diabetes, and people with diabetes without liver cirrhosis assumed the slopes were equal. The equality of the slopes was assessed by testing the glucose × group interaction term in a general linear model for HbA$_{1c}$, with glucose as a covariate and the group as a factor.

The correlation grid shows results for 27 people with diabetes and liver disease, and 123 with diabetes without liver disease (Fig. 2). Correlations for people with co-existing liver cirrhosis and diabetes are shown in the area of the grid above the diagonal and, for people with diabetes without liver cirrhosis, below the diagonal. The colour of the circles indicates whether the correlations are positive or negative. The intensity of the colour and the size of the circle are proportional to the correlation coefficients [17].

Pearson coefficients were calculated for pairwise groupings of each variable within the group, and displayed using the CORRPLOT package in the R program v. 0.84 [17]. Correlation coefficients were then compared using the R psych package v 1.7.8 [18]. Fisher transformations of correlation matrices were created to compare correlation coefficients within and between groups (psych::r.test function), and also when testing the independence of the two groups (psych::corrtest function).

Significance tests were performed by establishing the Z-score for the difference between the Fisher Z-transformed correlations when divided by the standard error of the difference between the two Z-scores. To confirm the assumption that the groups are two distinct populations, separable by the variables measured, a test of equivalence of the Fisher Z-score equivalents of the two correlation matrices was performed, which indicated two distinct groups (P<1.2e-06, Z-score of differences = 4.98).

The profile of the participant with α-1-antitrypsin-related liver disease was summarized graphically by expressing each value as a multiple of the median value for that variable in the group of people with diabetes without liver cirrhosis. The median values for the people with co-existing cirrhosis and diabetes disease (excluding the person with α-1-antitrypsin-related liver disease) were plotted similarly, Fig. 3.

Results

Characteristics of participants

There were no significant differences in age, gender or ethnicity, but serum creatinine was significantly lower in people with diabetes and cirrhosis (P=0.001, Table 1). Two distinct populations were identified when all the variables were considered (P<0.001).

Glucose and HbA$_{1c}$

Random plasma glucose concentrations did not differ, but HbA$_{1c}$ was substantially lower in people with liver disease:

Table 1 Characteristics of people with liver cirrhosis and diabetes awaiting transplant vs people with diabetes but no liver disease

	Reference range	People with cirrhosis and diabetes	People with diabetes and no liver disease	*P*
N		29	125	
Age, years		55 (49–63)	60 (50–71)	0.13
Men, *n* (%)		21 (72)	86 (69)	0.82
Ethnicity, *n*				
White European		27	94	0.20
South Asian		2	16	
Afro-Caribbean		0	10	
Other		0	5	
Severity of disease				
MELD score	<6	12 (9–17)*		
Creatinine†, μmol/l		77 (63–110)	98 (86–112)	0.001
Glycaemic markers				
Random plasma glucose, mmol/l		8.4 (7.2–11.2)	7.3 (5.3–11.5)	0.17
HbA_{1c}, mmol/mol	<48	41 (32–56)	61 (52–70)	<0.001
%	<6.5	5.9 (5.1–7.3)	7.7 (6.9–8.6)	
Haematology				
Red blood cell count, $\times 10^{12}$/l	Men: 4.2–5.7 Women: 3.8–5.1	3.6 (3.0–3.9)‡	4.7(4.3–5.0)	<0.001
Haemoglobin, g/l	Men: 135–180 Women: 115–165	106 (93–122)‡	137 (125–147)	<0.001
Haematocrit, l/l	Men: 0.40–0.54 Women: 0.37–0.47	0.32 (0.27–0.35)‡	0.40 (0.38–0.43)	<0.001
Mean cell volume, fl	80–99	91 (85–96)	86 (83–89)	0.001
Mean cell haemoglobin, pg	27–33	31 (28–33)	30 (28–31)	0.028
Mean cell haemoglobin concentration, g/l	315–365	339 (327–349)	341 (329–350)	0.473
Red cell distribution width, %	11–14	17 (15–18)*	13 (13–14)	<0.001
Reticulocyte count, $\times 10^9$/l	20–80	61 (47–71)	45(37–64)	0.005
Platelets, $\times 10^9$/l	150–450	103 (78–153)‡	251 (214–289)	<0.001
White cell count				
White cell count, 10^9/l	4.0–11.0	5.1 (4.3–6.8)	7.2 (6.2–8.8)	<0.001
Neutrophils, 10^9/l	2.0–7.5	3.4 (2.6–4.4)	4.3 (3.5–5.7)	0.002
Lymphocytes, $\times 10^9$/l	1.0–4.0	1.1 (0.7–1.3)	2.1 (1.8–2.5)	<0.001
Monocytes, $\times 10^9$/l	0.2–0.8	0.5 (0.4–0.6)	0.6 (0.4–0.7)	0.064
Eosinophils, $\times 10^9$/l	0.0–0.4	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.444

Median (IQR) interquartile range; otherwise *n* or %.
*Median higher than reference range. †Creatinine reference ranges dependent on age and gender. ‡Median lower than reference range.

median (IQR) 41 (32–56) mmol/mol [5.9 (5.1–7.3)%] vs 61 (52–70) mmol/mol [7.7(6.9–8.6)%]; (P<0.001, Table 1 and Fig. 1).

HbA_{1c} and glucose were positively correlated: r^2=0.34 in those with liver disease and r^2=0.30 in those without (P<0.001). Linear regression equations are cited in mmol/mol (IFCC) and % (Diabetes Control and Complications Trial/UK Prospective Diabetes Study) units:

liver disease: (mmol/mol) $HbA_{1c} = 3.0 \times RPG + 15.5$; or (%) $HbA_{1c} = 0.27 \times RPG + 3.6$

no liver disease: (mmol/mol) $HbA_{1c} = 1.8 \times RPG + 46.3$; or (%) $HbA_{1c} = 0.17 \times RPG + 6.4$,

where RPG is random plasma glucose. There was a significant difference of 20 mmol/mol (1.8%) HbA_{1c} (P<0.001) between the intercepts, assuming the slopes to be equal (P=0.12). A similar result was obtained when the data were restricted to white European people.

Haematology

There were major haematological differences between the groups, with fewer red blood cells, and lower haemoglobin and haematocrit levels in the group with diabetes and cirrhosis; with the median values lower than the reference ranges (Table 1). The red blood cell distribution width was higher in those with liver disease and above the reference range. The equivalent values for those with diabetes but no cirrhosis were within the reference ranges. Higher values for mean red blood cell volume and mean red blood cell haemoglobin were found in the group with diabetes and cirrhosis, indicating larger red blood cells, and also a higher reticulocyte count, indicating a shorter half-life. People with

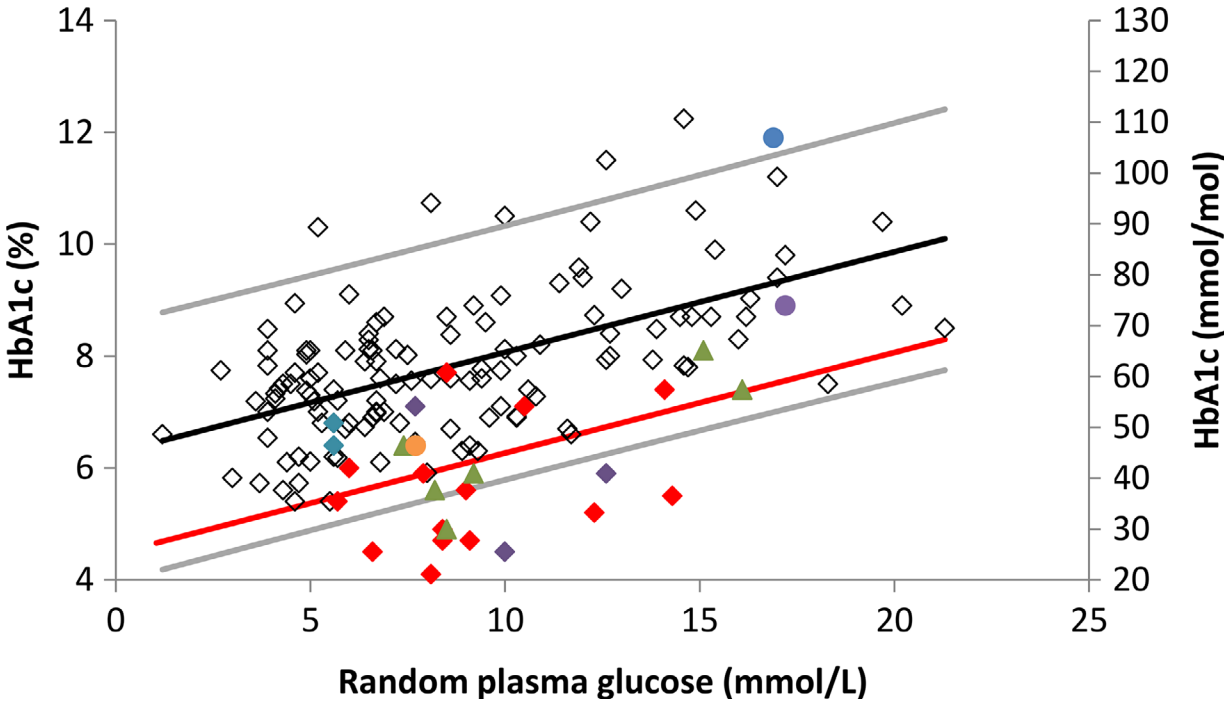

FIGURE 1 HbA$_{1c}$ and random plasma glucose in people with diabetes with cirrhosis awaiting liver transplant and without liver disease. The person with α-1-antitrypsin-related liver disease (blue circle) was excluded from further analyses. White diamonds: no liver disease; purple diamonds: alcoholic liver disease; red diamonds: non-alcoholic fatty liver disease; green triangles: hepatitis C; orange circle: polycystic liver and kidneys; blue diamonds: hereditary haemochromatosis; blue circle: α-1-antitrypsin-related liver disease; purple circle: cryptogenic/non-cirrhotic portal hypertension. Regression line black: no liver disease; regression line red: cirrhosis. 2SD lines: no liver disease.

diabetes and cirrhosis had fewer white blood cells, platelets and lymphocytes with no difference in eosinophils; all these counts were within the reference ranges in both groups.

Associations among variables

Further investigation was undertaken to determine the factors related to the depression of HbA$_{1c}$ in those with cirrhosis using a correlation grid (Fig. 2).

There were significant differences in the magnitude and direction of correlation coefficients for glucose between the groups: with mean cell haemoglobin: r=–0.092 (95% CI –0.265, 0.064) vs r=0.488 (95% CI 0.133, 0.732; P=0.010) in the diabetes without cirrhosis group vs the diabetes and cirrhosis group, respectively; mean cell haemoglobin concentration: r=–0.110 (95% CI –0.281, 0.069) vs r=0.363 (95% CI –0.018, 0.653), respectively (P=0.003, Fig. 2).

The correlation coefficients for HbA$_{1c}$ or glucose with the haematological variables showed statistically significant differences in the group with diabetes and cirrhosis. The correlation coefficients were positive for glucose, and negative or near zero for HbA$_{1c}$ for: (1) mean cell volume: HbA$_{1c}$, r=–0.278 (95% CI –0.595, 0.114); glucose, r=0.387 (95% CI 0.225, 0.528; P=0.020); (2) mean cell haemoglobin: HbA$_{1c}$, r=–0.260 (95% CI –0.583, 0.132); glucose, r = 0.488 (95% CI 0.341, 0.612; P = 0.010); (3) mean cell haemoglobin concentration: HbA$_{1c}$, r=–0.095 (95% CI –0.458, 0.296); glucose, r=0.363 (95% CI –0.018, 0.653); (P =0.049, Fig. 2).

When stepwise regression models were applied in those with diabetes and liver disease, red blood cell count and eosinophils had an R^2 value of 45.7% for HbA$_{1c}$, and mean cell haemoglobin and eosinophils an R^2 value of 39.9% for glucose. The most important factor determining HbA$_{1c}$ in people with diabetes but no liver disease was glucose.

Severity of liver disease

The median (interquartile range) Model for End Stage Liver Disease (MELD) score for the study cohort was calculated as 12 (9–17), (normal <6) in those with cirrhosis. The MELD score in people with co-existing liver cirrhosis and diabetes was negatively correlated with HbA$_{1c}$ (r=–0.56) and red blood cell count (r=–0.60). The correlation with glucose was r=–0.12, but MELD was positively correlated with mean cell haemoglobin, (r=0.32) and red cell distribution width (r=0.41).

α-1-antitrypsin disorder

The person with cirrhosis and diabetes related to α-1-antitrypsin disorder had high HbA$_{1c}$ relative to glucose, with HbA$_{1c}$ elevated by 28 mmol/mol (2.6%), (Fig 1). Their

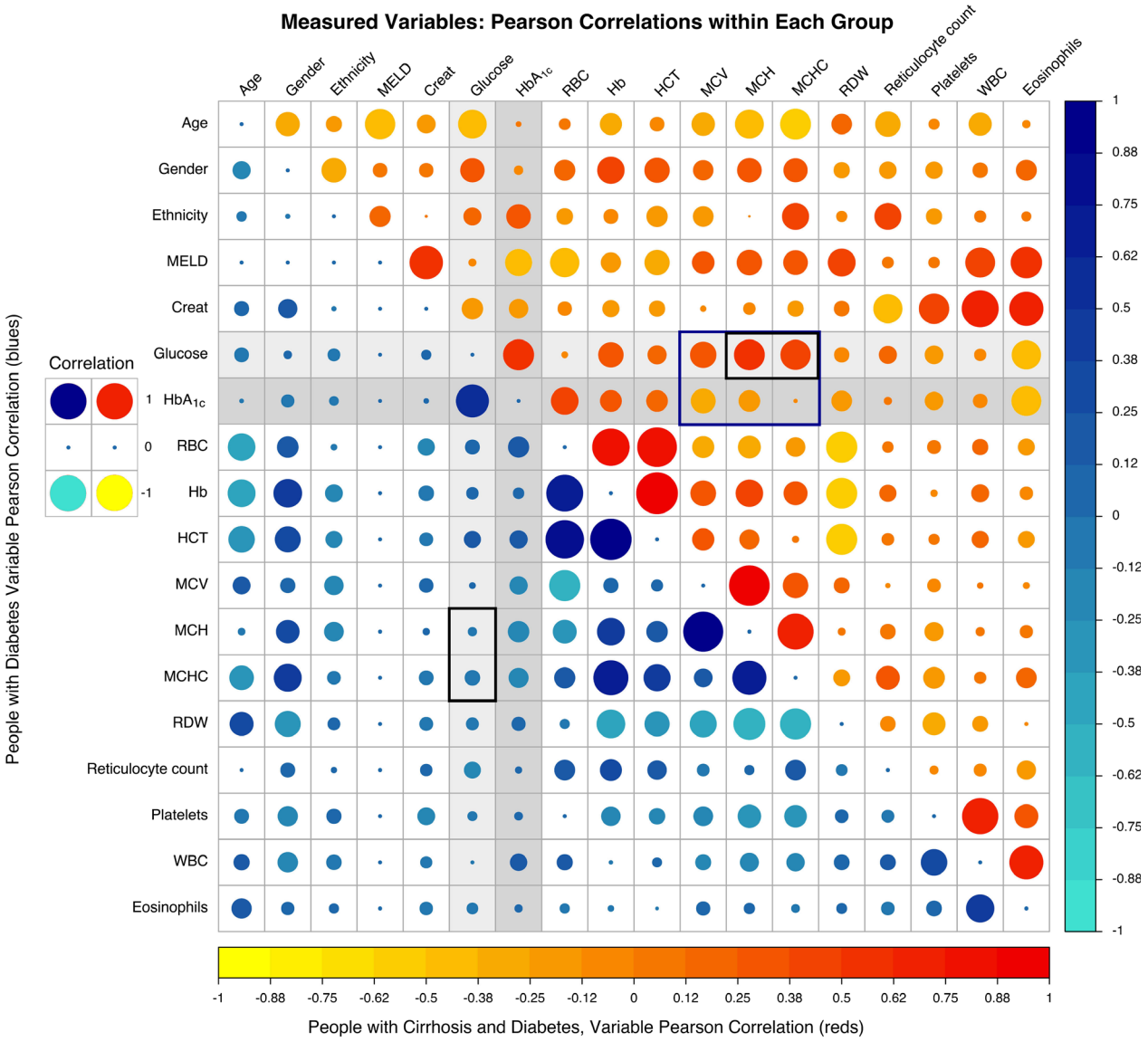

FIGURE 2 Relationships of characteristics of people with cirrhosis and diabetes awaiting liver transplant, and those with diabetes. Triangles: upper for those with liver disease, positive correlation coefficients, red and negative yellow; lower for those without liver disease, dark blue and cyan, accordingly. Circle size, largest for correlation +1 or –1; smallest if no correlation, i.e. 0. Shading: darker, HbA_{1c}; lighter, glucose. Box outlines: dark blue for statistically significant differences between HbA_{1c} and glucose correlations ($P<0.05$). Black for significant differences in correlations for glucose with variables. MELD, Model for End Stage Liver Disease; RBC, red blood cell count; Hb, haemoglobin; HCT, haematocrit; MCV, mean cell volume; MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration; RDW, red cell distribution width; WBC, white blood cell count.

haematological profile was different from that of the other people with cirrhosis and those without cirrhosis. The plot of haematological data for the person with α-1-antitrypsin disorder and for others awaiting transplant (as a multiple of the median for the group without liver disease) shows the differences in their anaemic profiles (Fig. 3).

Discussion

Cirrhosis of the liver in people with diabetes awaiting a liver transplant renders HbA_{1c} unsuitable for assessing blood glucose. In all but one person, it was associated with fewer, larger, more irregular red blood cells. A substantial depression in HbA_{1c} [20 mmol/mol (2%)] was observed relative to those with diabetes but no cirrhosis across a wide range of glucose values. This probably reflects a shorter red blood cell half-life and less exposure of haemoglobin to glucose. In contrast, the person with cirrhosis related to α-1-antitrypsin disorder had a higher HbA_{1c} level relative to glucose, with no factors indicating anaemia, suggesting the red blood cell half-life might be longer with more exposure to glucose.

This effect on HbA_{1c} in people with cirrhotic liver disease will cause misdiagnosis of diabetes and inappropriate clinical care. In our routine clinical practice, many more depressed

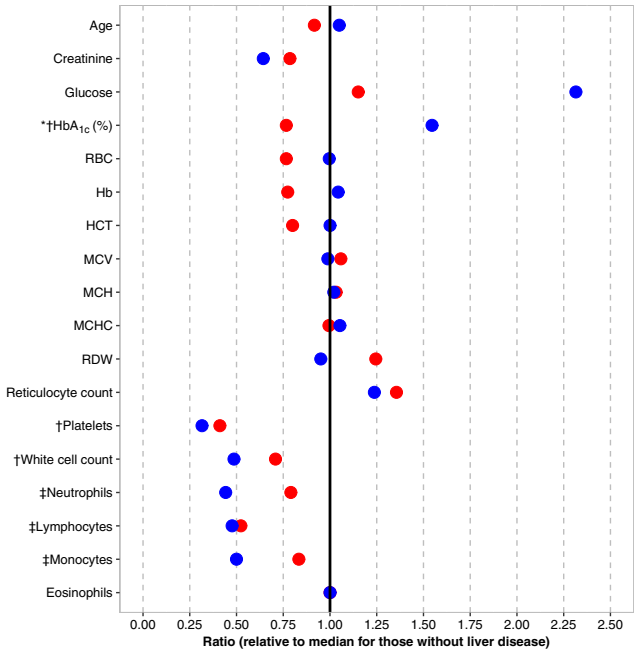

FIGURE 3 Comparison of haematology in people with diabetes and cirrhosis vs those with diabetes without liver disease. Circles: red for people with diabetes and cirrhosis, except for one person with α-1-antitrypsin disorder, which is blue. *P<0.01 for blue vs red; †P<0.01and ‡P<0.05 for blue vs people with diabetes without liver disease. RBC, red blood cell count; Hb, haemoglobin; HCT, haematocrit; MCV, mean cell volume; MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration; RDW, red cell distribution width.

than elevated HbA$_{1c}$ results have been noticed. We previously reported overtreatment resulting in hospital admission in one individual with known thalassaemia as a result of elevated HbA$_{1c}$ relative to glucose levels [12]. HbA$_{1c}$ assays do not identify thalassaemia, although some HbA$_{1c}$ analysers identify variant haemoglobins (e.g. S, F, C, D, E or rarer types) on chromatograms.

A recent US study in 200 people (62 with diabetes) referred for liver transplantation with decompensated cirrhosis showed similar depression in HbA$_{1c}$ relative to glucose [13]. HbA$_{1c}$ calculated from previous glucose results and compared to measured HbA$_{1c}$ [19], was found to be discordant by >0.5% in 49% of participants and >1.5% in 12% overall. Multivariate model analysis found haemoglobin to be the only independent predictor of the larger HbA$_{1c}$ discrepancies. More evidence is required regarding the extent of the effects of liver disease on the accuracy of HbA$_{1c}$ for clinical guidelines to improve on the diagnosis of diabetes and its management.

The groups differed distinctly when their biochemistry and haematology were compared, (Table 1 and Figs 2 and 3). The relationships of glucose and HbA$_{1c}$ to red blood cell haematology in people with diabetes and cirrhosis were markedly different from those in people with diabetes but no cirrhosis (Fig. 2). Low haemoglobin and macrocytosis evident in those with cirrhosis and diabetes were associated with depression in HbA$_{1c}$. The exception being the person with α-1-antitrypsin disorder whose erythrocytes did not display these features and whose HbA$_{1c}$ was elevated relative to glucose level. Anaemia can result in either shorter or longer erythrocyte lifespans and even differences in normal red blood cell morphology have been shown to affect the accuracy of HbA$_{1c}$ [20].

Any suspected inaccuracy in HbA$_{1c}$ can be confirmed using fructosamine, unless proteinuria is present [21], and point-of-care blood glucose testing or non-invasive continuous blood glucose devices. The data presented on >100 people attending the diabetes centre (along with corresponding fructosamine results) are used in our hospital to identify any outliers in glycaemic markers. As such, an elevated HbA$_{1c}$ relative to glucose level shows when additional testing, such as fructosamine/continuous blood glucose monitoring, should be organized by clinicians to confirm whether HbA$_{1c}$ is suitable for assessing glycaemic status. Monitoring glycaemia during the post-liver-transplant period is also an issue, as it is well known that post-transplant anaemia renders HbA$_{1c}$ unsuitable for clinical interpretation for ~6 months [5,22]. It is not known if this problem is resolved after liver transplantation.

Limitations of this study include the small number of people (29) studied with cirrhosis and diabetes compared to the available sample with diabetes but no cirrhosis (125). This sample size may hinder its ability to demonstrate statistical differences between the slopes of the regression lines. HbA$_{1c}$ was depressed by 25 mmol/mol (2.3%), (P<0.001), when the study was limited to age-matched white

European people with liver disease (mean age 55.6 years) compared to those without liver disease (mean age 55.3 years). As most of the participants were white European, it cannot throw any light on the current discussion about the relationship of HbA_{1c} to glucose by ethnicity [23]. Although random plasma glucose was measured rather than fasting, this reflects routine hospital practice as is evident in other studies [10]. Its measurement on glucose meters or blood gas machines quality-assured by the laboratory, or measured in the laboratory, is a quality indicator at the hospital. The number of people studied pre-transplant was small but it should be noted that the clinical audit was generated by observations of inaccurate HbA_{1c} in people with liver disease by experts in glycaemic markers over several years of routine clinical practice. Meta-analyses of small studies are common, with confirmatory studies required for clinical guidelines. Future research by our group will include more people with conditions that affect HbA_{1c} as outlined by WHO on more than one clinic visit [6].

In conclusion, cirrhosis of the liver affects the accuracy of HbA_{1c} results, leading to unreliable estimates of blood glucose over the previous 2 to 3 months. Anaemia in people with cirrhosis awaiting liver transplant is associated with altered red blood cell morphology. Significantly depressed HbA_{1c} was observed in all but one person with cirrhosis, along with lower haemoglobin level and fewer, larger, less uniform red blood cells. Visual representation of HbA_{1c} and random plasma glucose, along with haematology, is useful for assessing whether HbA_{1c} is accurate in individuals with coexisting illnesses or on drug regimens that affect red blood cells. Treatment targets for HbA_{1c} arising from clinical trials in diabetes [24,25] and cut-off values for diagnosis [7,23,26] rely on the provision of HbA_{1c} values that reflect circulating glucose.

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Competing interests

None declared.

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Data access statement

The datasets generated during and/or analysed during the study are not publicly available. The dataset contains clinical data which cannot be shared publicly as a result of UK data protection legislation.

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