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Fructosamine as a predictor of incident diabetic microvascular disease in a population with high prevalence of red cell disorders: A cohort study

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ABSTRACT

Aims: Fructosamine can be used to estimate glycaemia in individuals in whom HbA1c may be unreliable. We aimed to establish clinically useful fructosamine treatment targets in a population with a high prevalence of conditions affecting erythrocyte survival, including variant haemoglobin and G6PD deficiency.
Methods: Fructosamine was measured on a clinical basis in individuals in whom HbA1c was suspected to be unreliable by their primary physician. Study endpoints were incident retinopathy and albuminuria in individuals with Prediabetes (n = 60), Type 1 (n = 161) or Type 2 diabetes (n = 1350) during follow up of 4.4 ± 2.3 years.
Results: Fructosamine ≥ 250 umol/L was significantly associated with incident retinopathy, and fructosamine ≥ 300 umol/L with incident microalbuminuria, in univariate analysis and adjusted for established risk factors. Fructosamine ≥ 250 umol/L was also significantly associated with incident retinopathy in individuals with HbA1c < 7.0% (53 mmol/mol) at inclusion.
Conclusions: In this patient population, a single measurement of fructosamine significantly and independently predicts incident retinopathy in individuals with HbA1c < 7.0% (53 mmol/mol). Routine measurement of fructosamine on at least one occasion is recommended as part of assessment of prediabetes or diabetes mellitus in populations with a high prevalence of conditions affecting erythrocyte lifespan.

1. Introduction

Glycosylated haemoglobin (HbA1c) is the standard measure by which glycaemic exposure is monitored in people with diabetes mellitus, and well established in clinical practice as a risk marker for micro- and macrovascular complications in the majority of patients. However, HbA1c measurement may be confounded by coexisting haemoglobinopathy or other factors affecting red cell turnover [1], leading to suboptimal glycaemic control [2–4]. Fructosamine is an alternative marker for glycaemic control based on glycation of serum proteins which is less affected by red cell turnover [5,6]. Previous studies have shown that fructosamine is strongly associated with microvascular complications of diabetes and may add prognostic information to HbA1c in the general population [5,7]. Fructosamine is more closely correlated with CGM-estimated average glucose than HbA1c in patients with type 2 diabetes and end-stage renal disease receiving peritoneal dialysis [8].

In our clinical practice fructosamine is measured where HbA1c is inconsistent with either clinical outcomes or concomitant self-reported capillary blood glucose monitoring, or where a coexistent haemoglobinopathy or red cell fragility syndrome has been diagnosed and there is therefore reason to suspect that HbA1c is unreliable. However, clinical interpretation of fructosamine is challenging due to a lack of direct evidence-based targets for fructosamine levels. In previous reports, fructosamine is well correlated with HbA1c (r = 0.80) [9,10] and consequently in clinical practice fructosamine is commonly converted to an estimated HbA1c value for interpretation, potentially leading to loss of precision in risk estimates and clinical uncertainty. While average glucose can be estimated using continuous or flash glucose monitoring, the use of these systems is limited by cost and availability of consumables. Consequently, target ranges for fructosamine which have been validated against hard clinical endpoints remain desirable.

The internationally-approved diabetes target of HbA1c < 7.0% (53 mmol/mol) is defined by the inflection point at which the prevalence of diabetic retinopathy and risk of retinopathy progression begins to increase sharply [11], balanced against hypoglycaemia risk, but no equivalent cut-off has been validated for fructosamine. Fructosamine thresholds which indicate an increased risk of early diabetes-associated

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renal disease have also not been established.

The primary objective of this study is to characterize the utility of a single measurement of fructosamine in prediction of prevalent and incident microvascular complications in a population of people with prediabetes, type 2 diabetes or type 1 diabetes. The secondary objective is to supply estimates of risk of microvascular complications according to fructosamine level which can be used to set clinical targets in patients where HbA1c is unreliable.

2. Methods

2.1. Study population

Participants were recruited from Imperial College London Diabetes Centre (ICLDC), an outpatient facility with branches situated in Abu Dhabi and Al Ain in the United Arab Emirates. ICLDC provides primarily Diabetes and Endocrine care but also has clinics specialising in general medicine, cardiology, nephrology and ophthalmology. Patients attending ICLDC are predominantly of Arab Emirati origin. Fructosamine was measured as part of clinical practice where the patient's managing physician suspected a potential mismatch between HbA1c and either lab-measured fasting glucose or self-monitored capillary or interstitial blood glucose. The study received ethical approval from the ICLDC Research Ethics Committee (IREC061) and was carried out according to the principles of the Declaration of Helsinki.

2.2. Study design and criteria for inclusion

The study used a retrospective cohort design with longitudinal follow-up of individuals using the electronic medical record. Participants were included under ICLDC's General Consent for use of anonymised clinical data. The study was approved by ICDLC's institutional REC (IREC 061) and was carried out according to the principles of the Declaration of Helsinki. Inclusion criteria were a measurement of fructosamine performed at ICLDC and pre-existing diagnosis of prediabetes, type 1 diabetes or type 2 diabetes. The first recorded fructosamine measurement for each individual was included in analysis and the date of first fructosamine measurement was considered to be the date of inclusion. Prediabetes and diabetes mellitus were distinguished according to American Diabetes Association thresholds for HbA1c. Exclusion criteria were diagnosis of secondary diabetes, monogenic diabetes, or unknown diabetes type or glycaemic status. Blood pressure was measured using an automated system by trained nurses. Characteristics of the 1571 included participants are presented in Table 1.

2.3. Biochemical parameters

Fructosamine was assayed using Cobas 6000, c501 module (Roche) at ICLDC's clinical laboratory. The provided reference ranges for fructosamine are 205–285 umol/L in healthy normoglycaemic individuals and 228–568 umol/L in individuals with poorly controlled diabetes. Lipid parameters were measured using the Cobas platform (Roche). HbA1c was measured using the VARIANT II assay (BioRad). To establish clinically useful cut-offs for fructosamine reflecting changes in microvascular complication risk, participants were grouped by strata of fructosamine level approximating to quintiles rounded to the nearest 50 umol/L, defined as $\leq$ 249 umol/L, 250–299 umol/L, 300–349 umol/L, 350–399 umol/L and $\geq$ 400 umol/L. Strata for discretization of HbA1c were set at $\leq$ 5.9% (41 mmol/mol), 6.0–6.9% (42–52 mmol/mol), 7.0–7.9% (53–63 mmol/mol), 8.0–8.9% (64–74 mmol/mol) and $\geq$ 9.0% (75 mmol/mol).

Table 1
Participant characteristics stratified by glycaemic status. sBP = systolic blood pressure, MCV = mean corpuscular volume, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, TG = triglyceride.

	Prediabetes	Type 1	Type 2
Sample size (n)	60	161	1350
Female (%)	60.0 %	50.9 %	50.8 %
Age (years)	46.3 ± 11.4	25.9 ± 10.2	54.7 ± 12.9
sBP (mmHg)	123.2 ± 17.4	114.2 ± 22.4	126.9 ± 16.8
HbA1c (%)	5.4 ± 0.8	7.6 ± 2.1	6.7 ± 1.5
Fructosamine (umol/L)	239.6 ± 28.2	387.0 ± 103.3	297.1 ± 62.4
Hb (g/L)	127.3 ± 18.4	126.4 ± 15.5	126 ± 17.2
MCV (fl)	79.6 ± 11	78.0 ± 8.4	79.1 ± 8.7
HDL-C (mmol/L)	1.3 ± 0.3	1.5 ± 0.4	1.2 ± 0.3
LDL-C (mmol/L)	3.2 ± 0.9	2.8 ± 0.8	2.3 ± 0.9
TG (mmol/L)	1.4 ± 0.8	1.1 ± 0.9	1.6 ± 1

2.4. Haemoglobinopathy classification

Classification of anaemia, haemoglobinopathy and chronic haemolytic conditions in the study population was based on clinical investigations and in some cases was incomplete. Anaemia was defined as Hb < 125 g/L in males and < 115 g/L in females per local reference ranges, in the absence of haemoglobinopathy diagnosis or documented G6PD deficiency. Three patients had a documented diagnosis of haematological malignancy. Patients in whom haemoglobin electrophoresis indicated a haemoglobin variant were classified as "Variant Hb". Patients in whom more than 40% of all G6PD measurements were below the reference range, or where a diagnosis of G6PD deficiency had previously been established, were classified as "G6PD". Patients with both variant haemoglobin and G6PD deficiency were classified as "Variant + G6PD". Patients without haemoglobinopathy or G6PD deficiency but with chronic kidney disease (eGFR < 60 ml/min/1.73 m2) were defined as "Renal anaemia". Individuals with hypochromasia and ferritin < 20 were defined as having "Iron deficiency". Patients who were not classifiable into the preceding groups but who had persistent anaemia or microcytosis were defined as "Unclear". Among individuals in whom haemoglobin electrophoresis had been performed, four were diagnosed with thalassaemia major, eight with sickle cell anaemia and five with sickle beta thalassaemia. A summary of baseline characteristics of the participants and treatments used for management of anaemia, grouped by anaemia category, are presented in Table 2 and details of haemoglobin variants detected by haemoglobin electrophoresis are presented in Supplementary Table 1.

2.5. Study endpoints

Digital retinal images were reported by trained retinal grading technicians or, in cases of diagnostic uncertainty or inadequate retinal views, by a Consultant Ophthalmologist. Retinal photographs were coded according to the International Council of Ophthalmology classification (2014). Retinopathy was defined as any degree of retinal change including background disease or any degree of maculopathy. Onset of microalbuminuria was defined as urinary albumin-creatinine ratio (ACR) $\geq$ 3 mg/mmol and Albuminuria was defined as ACR of $\geq$ 30 mg/mmol per the National Kidney Foundation definition. ICLDC standard of care is that both digital retinal photography and urine ACR should be performed at least once per year. Endpoint data was available for a median of 4.83 (3.4–6.57) years from time of study inclusion.

2.6. Study power

The annual incidence of diabetic retinopathy has been estimated at 15.2% in individuals with type 1 diabetes and 8.1% in individuals with type 2 diabetes [12] while four-year cumulative incidence of retinopathy has been reported as 360.3 per 1000 individuals [13]. Over 4 years of follow up we would therefore expect between 332 and 480 new cases of retinopathy given a study population of 1000 individuals, allowing between 66 and 96 endpoints per pre-specified established risk factor of systolic blood pressure, triglyceride level, smoking and age in regression analysis.

Table 2
Participant characteristics stratified by anaemia diagnosis. Hb = haemoglobin, G6PD = glucose-6-phosphate dehydrogenase deficiency.

	No Anaemia	Iron Deficiency	Variant Hb	G6PD	G6PD + Variant Hb	Renal Cause	Haem.Malignancy	Unclear
All	879	185	183	116	17	140	3	48
Male	476	35	76	69	12	70	3	26
Female	403	150	107	47	5	70		22
Prediabetes	38	8	8	5		1		
Type 1 diabetes	87	18	21	21	5	6		3
Type 2 diabetes	754	159	154	90	12	133	3	45
Hb (g/L)	135.3 ± 13.3	107.1 ± 8.8	121.8 ± 17.0	120.6 ± 13.8	122.7 ± 15.4	109 ± 9.2	117.3 ± 8.0	113.1 ± 9.2
HbA1c (%)	6.7 ± 1.7	7.0 ± 1.7	7.0 ± 1.7	5.9 ± 1	5.8 ± 1	6.8 ± 1.4	6.9 ± 1.2	7.0 ± 2
Fructosamine (umol/L)	303.0 ± 71.3	289.4 ± 73.1	305.5 ± 82.7	320.9 ± 71.4	298.4 ± 73.4	307.5 ± 62.4	310.7 ± 9.9	325.2 ± 95.9
Oral iron	61	97	42	23	1	85	0	18
Intravenous iron	6	10	1	4	0	3	0	0
Testosterone	5	0	1	1	0	0	0	0
Vitamin B12	219	64	44	22	5	57	1	14
Erythropoietin	5	1	3	0	1	37	0	0
Roxadustat	0	0	0	0	0	3	0	0

2.7. Statistical analysis

Statistical analysis was performed using the R Language for Statistical Computing version 4.1.3 and the *survival, survminer* and *emmeans* packages. Data are presented as mean ± sd or median (interquartile range) as appropriate for distribution. Linear regression with an interaction term between HbA1c and anaemia group was used to assess the association between HbA1c and fructosamine in the study population. Logistic regression was used to assess odds of prevalent microvascular disease. Cox regression models, adjusted for relevant risk factors, were used to determine hazard ratios for higher fructosamine strata compared with the baseline level (see Biochemical parameters above). No correction for multiple comparisons was indicated for pre-planned analyses; Tukey correction was performed for post-hoc pairwise comparisons. Significance was set at $p < 0.05$.

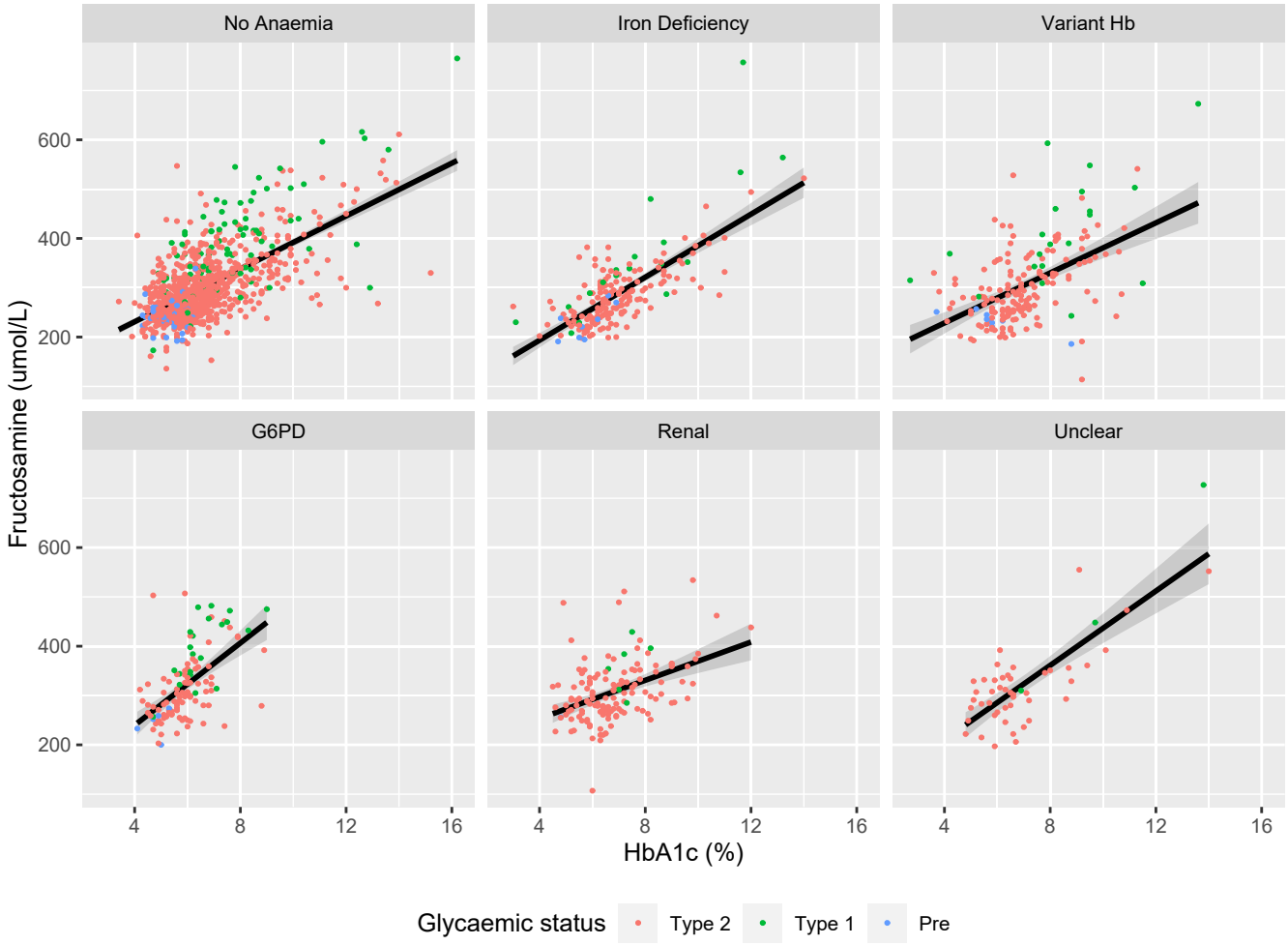

Fig. 1. Relationship between Fructosamine and HbA1c by anaemia and haemoglobinopathy status. Individuals with G6PD + Variant Hb or with haematological malignancy are omitted due to small group size. Lines represent linear regression of HbA1c on fructosamine and shaded areas represent a 95% confidence interval of fit.

3. Results

3.1. Weak relationship between fructosamine and HbA1c in the study population

In the study population, fructosamine was only weakly correlated with HbA1c and the slope of the relationship between fructosamine and HbA1c differed significantly between anaemia groups. In univariate linear regression, fructosamine was significantly but weakly associated with HbA1c ($r2 = 0.353$, $p < 0.0001$) in the study group as a whole. The haematological malignancy and G6PD + haemoglobinopathy groups were excluded from further analysis due to small group size. Both slopes and intercepts for the relationship between HbA1c and Fructosamine differed significantly between anaemia groups ($p < 0.001$ for the interaction term). Pairwise comparisons of effect of anaemia group on the relationship between fructosamine and HbA1c are presented in Supplementary Tables 2 and 4 and estimated slopes for the relationship between fructosamine and HbA1c for each anaemia group are presented in Supplementary Table 3. Relationships between fructosamine and HbA1c in each group are presented in Fig. 1 and distributions of fructosamine and HbA1c at inclusion for individuals with prediabetes, Type 1 diabetes, and Type 2 diabetes are presented in Supplementary Fig. 1.

3.2. Measures of glycaemia and prevalence of microvascular disease

3.2.1. Relationship between fructosamine or HbA1c and prevalent retinal disease

Prevalent retinopathy was defined as any degree of diabetic retinopathy reported prior to or equal to the date of fructosamine measurement. The prevalence of any degree of retinopathy at inclusion was 261 of 1571 (16.6%). Participants were grouped by 50 umol/L intervals of fructosamine from a baseline of ≤ 249 umol/L to a maximum of ≥ 400 umol/L. HbA1c was similarly grouped by 1% intervals from a baseline of < 6% to a maximum of ≥ 9%. Univariate relationships between fructosamine or HbA1c and retinopathy prevalence is illustrated in Fig. 2. Adjusting for age and diabetes type in logistic regression, all

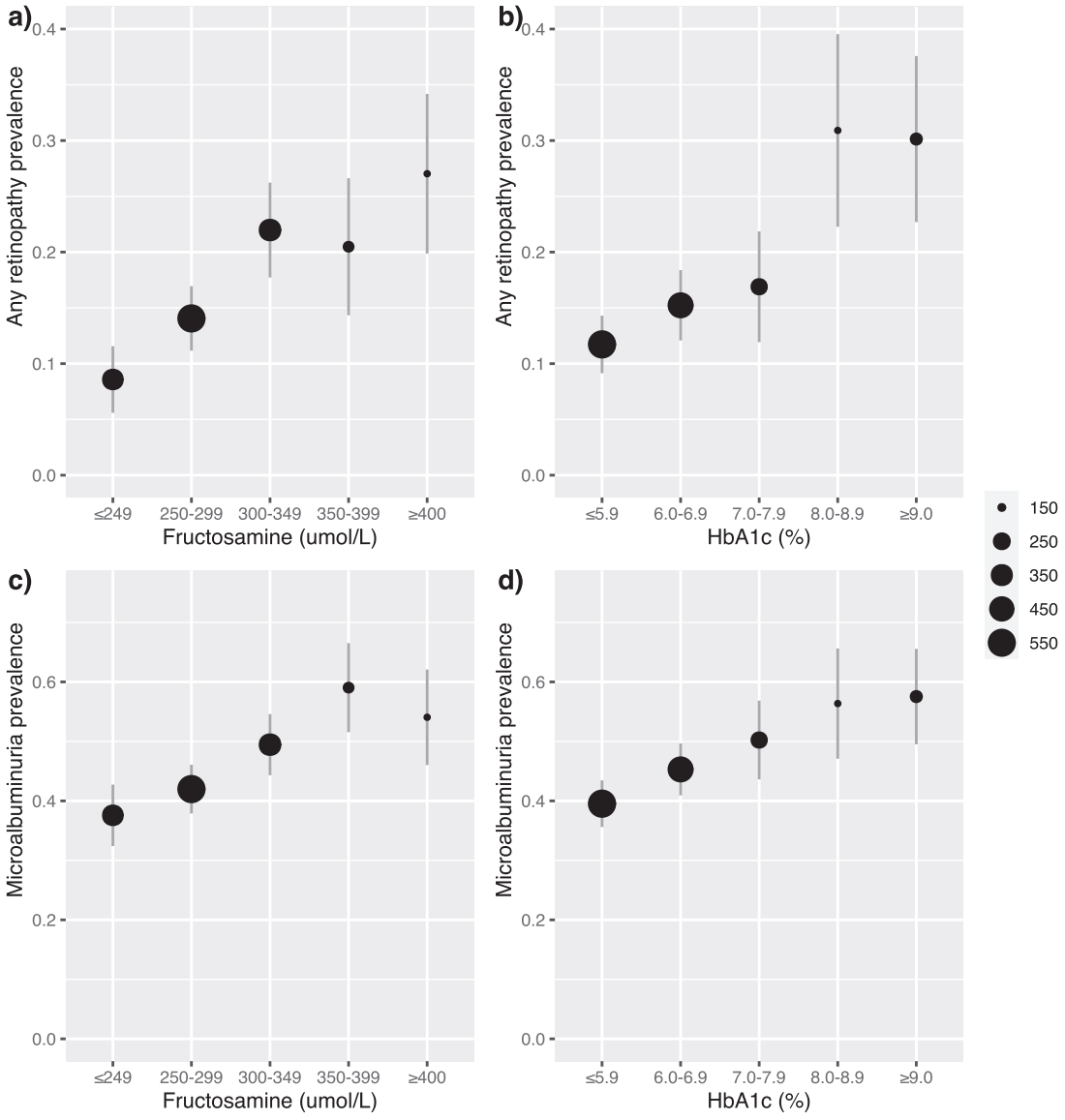

Fig. 2. Relationships between the prevalence of any degree of retinopathy and level of fructosamine or HbA1c for individuals with prediabetes, Type 1 diabetes, or Type 2 diabetes. Point size represents the number of individuals in each group. Confidence intervals represent the 95% confidence interval of the population mean. Plots: a) prevalence of diabetic retinopathy by fructosamine group, b) prevalence of diabetic retinopathy by HbA1c group, c) prevalence of microalbuminuria by fructosamine group, d) prevalence of microalbuminuria by HbA1c group.

strata of fructosamine ≥ 300 umol/L were associated with significantly increased odds of prevalent diabetic retinopathy when compared with baseline (odds ratios (OR): 250–299 umol/L 1.48 (0.95–2.37) p = 0.0919, 300–349 umol/L 2.47 (1.60–3.97) p = 0.0001, 350–399 umol/L 2.36 (1.37–4.10) p = 0.0020, ≥ 400 umol/L 4.036 (2.32–7.09) p < 0.0001). When compared with the baseline state of HbA1c < 6.0% (31 mmol/mol) and adjusted for age and diabetes type, all HbA1c strata with HbA1c 8.0–8.9% (64–74 mmol/mol) or above were associated with increased odds of diabetic retinopathy (OR: 6.0–6.9% 1.22 (0.85–1.73) p = 0.2802, 7.0%-7.9% 1.39 (0.89–2.14) p = 0.1420, 8.0–8.9% 3.24 (1.98–5.26) p < 0.0001, ≥ 9.0% 3.08 (1.97–4.77) p < 0.0001).

3.2.2. Relationship between fructosamine or HbA1c and prevalent microalbuminuria

Prevalent microalbuminuria was defined as urinary ACR ≥ 3.0 at the time of fructosamine measurement while prevalent albuminuria was defined as urinary ACR ≥ 30.0 at the time of fructosamine measurement. At inclusion, 718 (45.7%) of individuals met criteria for microalbuminuria and 187 (11.9%) met criteria for albuminuria. The relationships between fructosamine and HbA1c levels and prevalent microalbuminuria and albuminuria are presented in Fig. 2. Adjusting for age and diabetes type, the odds of prevalent microalbuminuria or albuminuria were significantly increased at fructosamine levels of ≥ 350 umol/L (ORs for microalbuminuria: 250–299 umol/L 0.97 (0.73–1.30) p = 0.8386, 300–349 umol/L 1.31 (0.95–1.80) p = 0.1023, 350–399 umol/L 2.18 (1.46–3.28) p = 0.0002, ≥ 400 umol/L 2.37 (1.53–3.69) p = 0.0001; ORs for albuminuria: 250–299 umol/L 1.13(0.70–1.89) p = 0.6241, 300–349 umol/L 1.50 (0.90–2.55) p = 0.1259, 350–399 umol/L 2.90 (1.65–5.16) p = 0.0003, ≥ 400 umol/L 2.15 (1.10–4.15) p = 0.0226). When compared with the baseline state of HbA1c < 6.0% (31 mmol/mol) and adjusted for age and diabetes type, all HbA1c strata above HbA1c 7.0–7.9% (53–63 mmol/mol) were associated with increased odds of prevalent microalbuminuria (OR: 6.0–6.9% 1.14 (0.89–1.46) p = 0.3135, 7.0%-7.9% 1.464 (1.06–2.03) p = 0.0223, 8.0–8.9% 2.06 (1.34–3.19) p = 0.0011, ≥ 9.0% 2.1 (1.43–3.10) p = 0.0002).

3.3. Measures of glycaemia and incident microvascular disease

3.3.1. Diabetic retinopathy

The relationship between measures of glycaemia and incident microvascular complications of diabetes was investigated using Cox proportional hazards models to control for covariates. Diabetes diagnosis was not a significant factor in any of the models and was excluded from analysis. Kaplan-Meier plots illustrating univariate relationships between measures of glycaemia and incident retinopathy and albuminuria in the study group are presented in Supplementary Figs. 2-5. Adjusted for age at enrolment, systolic blood pressure and smoking status, all fructosamine strata ≥ 250 umol/L were significantly associated with stepwise increased hazard of incident retinopathy (Hazard ratios; 250–299 umol/L 1.75 (1.18–2.60) p = 0.0058, 300–349 umol/L 2.22 (1.46–3.37) p = 0.0002, 350–399 umol/L 2.94 (1.85–4.65) p <

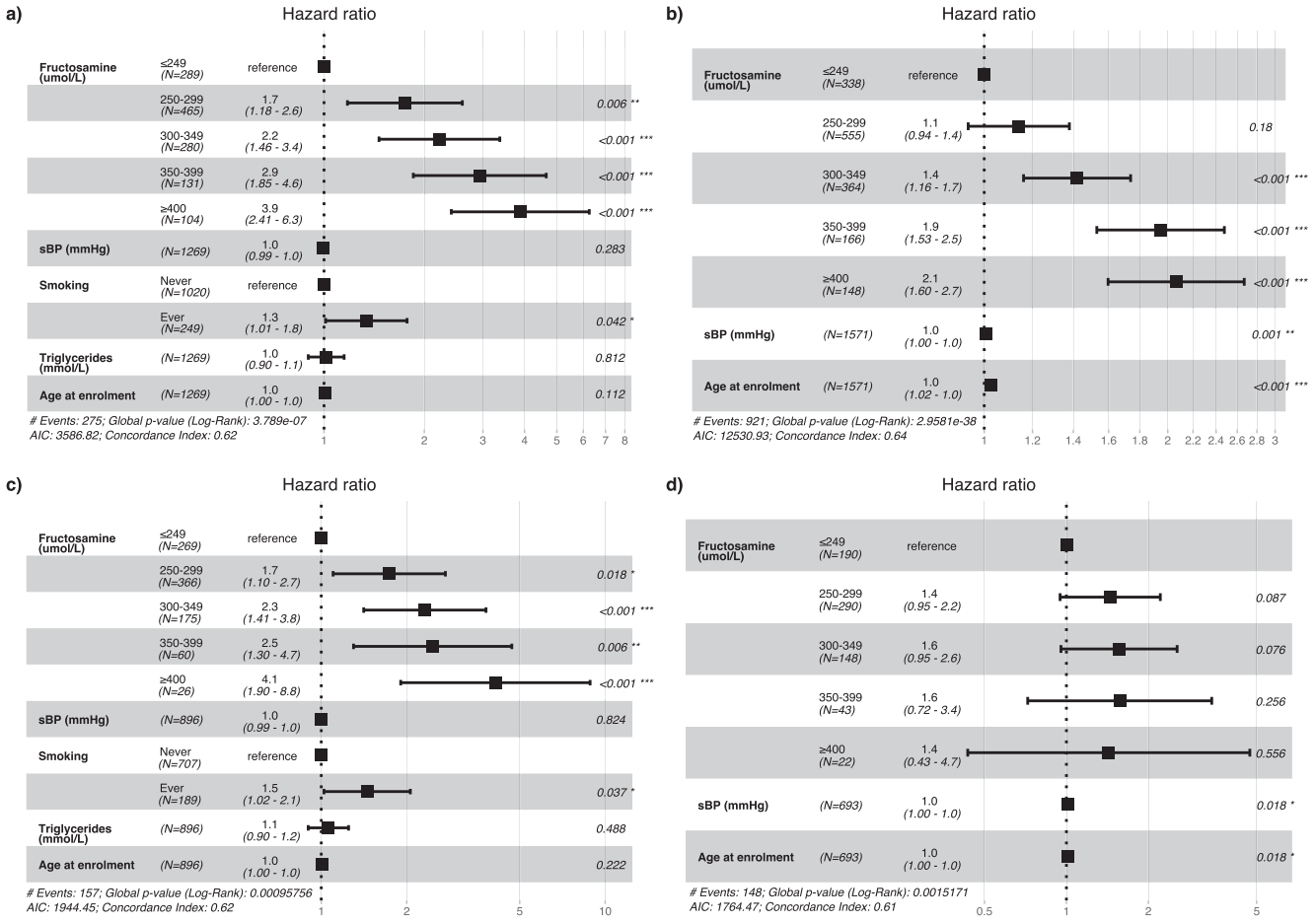

Fig. 3. Forest plots of incidence of any degree of retinopathy in individuals with prediabetes, Type 1 Diabetes or Type 2 diabetes, adjusted for systolic blood pressure. Panels: hazard ratios for a) diabetic retinopathy, b) microalbuminuria or albuminuria, c) diabetic retinopathy in individuals with HbA1c < 7.0% at time of fructosamine measurement, d) microalbuminuria or albuminuria in individuals with HbA1c < 7.0% at time of fructosamine measurement. sBP = systolic blood pressure.

0.0001, ≥ 400 umol/L 3.88 (2.41–6.26) p < 0.0001, see also Fig. 3**a**) in 1269 individuals without retinopathy at inclusion followed up for a mean duration of 4.4 ± 2.3 years. Adjusting for the same covariates, all HbA1c strata ≥ 6.0% (31 mmol/mol) were associated with increased hazard of incident retinopathy (Hazard ratios: 6.0–6.9% 1.43 (1.05–1.94) p = 0.0252, 7.0%-7.9% 2.01 (1.39–2.91) p = 0.0002, 8.0–8.9% 2.77 (1.74–4.42) p < 0.0001, ≥ 9.0% 3.59 (2.45–5.24) p < 0.0001).

3.3.2. Diabetic nephropathy

Adjusting for age at enrolment and systolic blood pressure, in 813 individuals without microalbuminuria at inclusion followed up for 4 ± 2.3 years, fructosamine levels ≥ 300 umol/L were significantly and independently associated with increased hazard of any degree of albuminuria (Hazard ratios; 250–299 umol/L 1.14 (0.94–1.38) p = 0.1805, 300–349 umol/L 1.42 (1.16–1.74) p = 0.0007, 350–399 umol/L 1.95 (1.53–2.48) p < 0.0001, ≥ 400 umol/L 2.07 (1.60–2.67) p < 0.0001, see also Fig. 3**b**). All HbA1c strata ≥ 7.0% (53 mmol/mol) were associated with increased hazard of incident nephropathy when compared (Hazard ratios: 6.0–6.9% 1.1 (0.94–1.29) p = 0.2435, 7.0%-7.9% 1.36 (1.11–1.67) p = 0.0030, 8.0–8.9% 1.66 (1.29–2.13) p < 0.0001, ≥ 9.0% 1.78 (1.42–2.24) p < 0.0001).

3.4. Predictive value of fructosamine where HbA1c < 7.0 %

In order to assess the potential usefulness of fructosamine as a measure of glycaemia where HbA1c is unreliable, we evaluated the ability of fructosamine to predict incident microvascular complications of diabetes in a subset of individuals with HbA1c < 7.0% (53 mmol/mol) at the time of fructosamine measurement. In 896 individuals without evidence of retinal disease at the time of inclusion, followed up for a mean of 4.5 ± 2.3 years, fructosamine strata ≥ 250 umol/L were significantly and independently associated with increased hazard of any grade of diabetic retinopathy, adjusted for age, systolic blood pressure and smoking status, when compared with fructosamine ≤ 249 umol/L (Hazard ratios; 250–299 umol/L 1.74 (1.10–2.74) p = 0.0176, 300–349 umol/L 2.32 (1.41–3.80) p = 0.0009, 350–399 umol/L 2.47 (1.30–4.69) p = 0.0058, ≥ 400 umol/L 4.11 (1.91–8.85) p = 0.0003, see also Fig. 3**c;** univariate association illustrated in **Supplementary Fig. 6**). However, adjusting for age and systolic blood pressure, none of the fructosamine strata were significantly associated with increased hazard of onset of any degree of albuminuria in 586 individuals without microalbuminuria at enrolment with microalbuminuria data covering for 4.1 ± 2.4 years after fructosamine measurement (Hazard ratios; 250–299 umol/L 1.45 (0.95–2.21) p = 0.0867, 300–349 umol/L 1.56 (0.96–2.55) p = 0.0757, 350–399 umol/L 1.57 (0.72–3.42) p = 0.2561, ≥ 400 umol/L 1.43 (0.43–4.72) p = 0.5560, see also Fig. 3**d**). This finding was not affected by further adjustment for exposure to an ACEI or ARB at time of fructosamine measurement.

4. Discussion

The relationship between HbA1c and the prevalence of microvascular complications is well established and informs the internationally accepted targets for glycaemic control in people with diabetes. Fructosamine has not been evaluated to the same extent and in clinical practice is usually converted to an HbA1c value for purposes of interpretation on the basis that the two are usually closely correlated [10]. Fructosamine is used to monitor short-term glucose control and when HbA1c measurements can be affected by altered erythrocyte turnover [9]. More recently, observational studies have also focused on the role of Fructosamine as a risk factor for cardiovascular complications. The association between Fructosamine and cardiovascular disorders has been recently described [5,7,10].

Fructosamine has previously been linked with prevalent diabetic retinopathy and with incident new onset diabetes and incident CKD3 in the ARIC cohort [5]. Our study builds on this work by using more frequent clinical screening evaluations to examine retinopathy incidence, and by relating fructosamine to microalbuminuria and albuminuria, earlier signs of diabetic kidney disease and an important standard of care in screening for diabetic nephropathy. We have additionally provided more detailed phenotyping of haemoglobinopathy in our cohort. Although our study was biased in that fructosamine was measured where considered clinically important, our findings were broadly consistent with the ARIC cohort.

Fructosamine, is associated with increased hazard of incident macrovascular disease both in patients with end-stage renal disease [14] and more general outpatient diabetes populations [7]. The current study was based at an outpatient diabetes facility and therefore information regarding macrovascular disease outcomes was expected to be incomplete, and a relatively small number of macrovascular events would be expected during the study follow-up period [15]. Consequently, we did not attempt to explore a macrovascular endpoint, although it should be noted that diabetic retinopathy is itself a risk factor for macrovascular disease [16].

Previous studies exploring the use of fructosamine in assessment of glycaemic control have predominantly been performed in populations where it is well correlated with HbA1c [9,10], raising the possibility that fructosamine might not be a useful predictor of diabetes complications in in situations where it does not correlate closely with HbA1c. In our study population, not only did fructosamine correlate poorly with HbA1c but also relationship between the two varied significantly between anaemia groups, potentially further confounding the use of conversion of fructosamine to estimated HbA1c for clinical interpretation. Our findings demonstrate that fructosamine is an independent predictor of incident microvascular complications of diabetes even when poorly correlated with HbA1c, reinforcing its clinical utility. We also provide quantitative estimates of the increase in relative microvascular risk associated with each 50 umol/L increase in fructosamine over 249 umol/L, which can be used to inform clinical decision making and patient education without requiring conversion to HbA1c for interpretation. Our findings support a recommend target fructosamine level of ≤ 249 umol/L, where achievable without hypoglycaemia, in order to minimise microvascular complications of diabetes.

Our study is the first, to our knowledge, to examine the use of fructosamine in evaluating the risk of incident retinal disease in people with prediabetes or diabetes. Additionally, we demonstrate that fructosamine provides comparable accuracy for prediction of retinopathy in a subset of our study population who, per their HbA1c, appeared to have achieved internationally-accepted targets for glycaemic control. Of note, the increase in hazard of retinopathy for each stratum of fructosamine in those individuals with an HbA1c < 7.0% at time of measurement was comparable with that of the entire study group. Although fructosamine did not predict nephropathy in patients with HbA1c < 7.0% in the current study, it has previously been established that diabetic retinopathy is itself a nephropathy predictor in both type 1 and type 2 diabetes [17–19]. The lack of significant association between fructosamine and incident microalbuminuria in this group is consistent with previous reports of weak correlation between fructosamine and glycaemic control in individuals with diabetes and chronic kidney disease [20]. However, the relatively high prevalence of microalbuminuria at inclusion limited the number of individuals in which the nephropathy incidence endpoint could be assessed and the possibility that fructosamine might significantly predict incident albuminuria in a group with a lower prevalence of microvascular complications can not be excluded.

4.1. Potential sources of bias

Fructosamine was measured on a clinical basis and is not a routinely performed test at ICLDC, introducing a significant element of selection bias into the study population. Fructosamine may have been more likely to have been assessed in patients where a haemoglobinopathy or other

chronic haemolytic condition was already known and there was clinical suspicion that HbA1c measurement was inaccurate. Investigations for haemoglobinopathies and G6PD deficiency were performed as part of clinical screening rather than a study protocol.

5. Conclusions

Fructosamine as measured using Cobas 6000, c501 module (Roche) predicts microvascular complications of diabetes, with a significantly increased risk of prevalent and incident disease at levels $\geq$ 250 umol/L when compared with fructosamine $\leq$ 249 umol/L. Fructosamine also appeared to stratify microvascular risk in patients who were ostensibly at their HbA1c target, justifying routine clinical use in populations with high prevalence of variant haemoglobin or red cell fragility disorders.

6. Contributors

CMI and AJB conceived the study. CMI and AJB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AJB and TA performed the literature search and drafted the manuscript. All authors contributed to revision and editing of the manuscript.

7. Funding

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8. Data statement

De-identified data that underlie the results reported in this article will be available for up to 5 years following publication for sharing with researchers who submit a study question which, in the opinion of the authors, can be addressed by the data. Enquiries should be directed to abuckley@icldc.ae. An institutional contract and data sharing agreement will be required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110873.

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