Evaluation of Fructosamine and Fructosamine-Albumin Ratio in Reflecting Fasting Glucose in Type 2 Diabetic Patients with Chronic Kidney Disease: A Case-Control Study

Tuan Manh Ha
University of Medicine and Pharmacy at Ho Chi Minh City
Thuy Thi Dao
University of Medicine and Pharmacy at Ho Chi Minh City
Anh Tuan Nguyen (anh.nt@umc.edu.vn)
Molecular Biomedical Center, University Medicine Center Ho Chi Minh City

Research Article

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Abstract

Background

Glycated haemoglobin (HbA1c) may not correctly reflect chronic glycaemic control in type 2 diabetes mellitus (T2DM) patients with chronic renal disease (CKD) due to anaemia. Growing evidence reports that fructosamine in reflecting glycaemic control is unaffected by anaemia in in these patients. However, the role of fructosamine remains unclear. Thus, this study aimed to evaluate the acceptance of HbA1c and determine whether fructosamine levels or fructosamine-albumin ratios might be promising biomarkers of glycaemic control in T2DM patients with or without CKD.

Methods

HbA1c and fructosamine levels were measured in 50 T2DM patients with CKD and 50 T2DM patients without CKD, together with 30 healthy subjects. The area under the curve and receiver operating characteristic curves were used to compare HbA1c, fructosamine levels, and fructosamine-albumin ratio in reflecting glycaemic control. Youden's index was applied to identify the cut-off points for those parameters. The cut-off point for HbA1c was 6.0%, which was used as the standard method to determine the values of fructosamine and fructosamine-albumin ratio predictors for complications.

Results

HbA1c levels correlated strongly with fasting blood glucose in T2DM patients without CKD ($r = 0.758$, $p < 0.01$) and moderately ($r = 0.575$, $p < 0.01$) in those with CKD. However, fructosamine levels and the fructosamine-albumin ratios showed a moderate correlation with fasting blood glucose in those without CKD ($r = 0.466$, $p < 0.01$ and $r = 0.436$, $p < 0.01$, respectively). Estimated blood glucose levels calculated by HbA1c were similar to actual fasting blood glucose in T2DM patients with different levels of eGFR. However, for fructosamine levels and fructosamine-albumin ratios, the estimated blood glucose levels were similar to actual fasting blood glucose in groups of T2DM patients with eGFR levels lower than 45 and 30 mL/min/1.73 m^2, respectively. The fructosamine-albumin ratio was a strong predictor of glycaemic control in T2DM patients with CKD (AUC = 0.923), comparable with HbA1c (AUC = 0.966). A fructosamine level of 270 μmol/L was identified as the optimal cut-off point for monitoring the response to T2DM treatment.

Conclusion

The fructosamine concentration or fructosamine-albumin ratio effectively reflected blood glucose levels in T2DM Vietnamese patients with CKD (eGFR levels lower than 45 and 30 mL/min/1.73 m^2, respectively).

Background

Type 2 diabetes mellitus (T2DM) is a public health issue, as its prevalence has increased over the last few decades. It is a long-term metabolic condition that causes significant damage to the heart, blood vessels, eyes, kidneys, and nerves [1]. Chronic kidney disease (CKD) is one of the common complications of diabetic patients which can lead to kidney failure, also known as end-stage renal disease (ESRD), requiring dialysis [1, 2]. It is known that control of blood glucose in patients with T2DM is an effective treatment to prevent diabetic complications, including CKD complications [3, 4]. Therefore, monitoring the glycaemic control in patients with T2DM is crucial in managing and preventing complications related to diabetes [2, 5].

Currently, the haemoglobin A1c (HbA1c) index is considered a standard test for monitoring the long-term (~ 3 months) glycaemic control of people with T2DM [6]. This index has been used as a significant indicator to reflect the cumulative blood glucose concentration throughout the preceding 8 to 12 weeks [7]. However, several factors can affect serum HbA1c levels, such as the amount of haemoglobin and its lifespan and high levels of urea in the blood [8]. Both anaemia (low haemoglobin) and uraemia (urea accumulation in the blood) are prevalent in T2DM patients with CKD. Thus, the HbA1c index may not reflect precisely in the process of blood glucose monitoring in these patients [9, 10]. It can be explained that anaemia often relates to the inability to produce adequate erythropoietin, which is accompanied by a decrease in glomerular filtration rate (GFR). As a result of reduced erythropoiesis, there are more circulating old red blood cells (RBCs) and a gradual increase in HbA1c, which is unrelated to glycaemic control [11, 12].

Fructosamine is known as stable ketoamine and is created by the reaction between glucose and albumins or other serum proteins through a process of protein glycation [13]. Growing evidence suggests that the concentration of fructosamine also reflects the blood glucose level over the previous 2 to 3 weeks and may better monitor short-term changes in glycaemia [3, 6, 13, 14]. In contrast to the HbA1c value in CKD patients, the fructosamine index does not depend on uraemia and anaemia [15]. However, fructosamine is generated from nonenzymatic glycation of serum protein, mainly albumin (~ 90%) [16]. Therefore, correcting fructosamine levels for serum albumin changes (fructosamine-albumin ratio) should also be noticed and evaluated [17, 18]. Recently, some studies have compared HbA1c and fructosamine to monitor the level of glycaemic control in patients with T2DM and CKD [5, 17, 19, 20]. However, the conclusion regarding the superiority of fructosamine over HbA1c remains unclear. For example, in a narrative review, Speeckaert *et al.* concluded that HbA1c is still the gold standard for monitoring long-term glycaemic control. However, its levels in patients with CKD may vary [8].

Meanwhile, Chen *et al.* reported that estimated average glucose measured from HbA1c and fructosamine levels might underestimate average blood glucose levels among patients with CKD stages 3–4 [17]. On the other hand, Bomholt *et al.* suggested using fructosamine for glycaemic monitoring in T2DM patients [9]. Controversies between studies may also result from different patient populations with diabetes and clinical complications, as suggested [21, 22]. Therefore, we aimed to investigate the significance of

HbA1c in Vietnamese T2DM patients and to identify whether the fructosamine level or fructosamine-albumin ratio could be used as reliable glycaemic control indicators instead of HbA1c in these patients with CKD to provide appropriate recommendations in clinical practice.

Methods

Study design and participants

This hospital-based case-control study recruited patients with T2DM who were frequency matched to controls by sex at a 1:1 ratio in the University Medical Center at Ho Chi Minh City - Campus 2 from October 2020 to April 2021.

Fructosamine and HbA1c levels were thus used to estimate the required sample size [9] (https://openepi.com/SampleSize/SSMean.htm). The levels of fructosamine and HbA1c in T2DM patients with CKD were approximately 395,28 ± 74,82 (μmol/g) and 7.4 ± 1.7 (%), respectively [2, 23]. Furthermore, we estimated that the fructosamine and Hb1Ac levels changed by approximately 15%. The effect size was set at a 5% level of significance. Thus, the sample size was rounded to 50 participants per group, indicating that 100 participants (50 T2DM cases with CKD and 50 T2DM controls without CKD) were needed.

In brief, participants over 18 years old who were diagnosed with T2DM were recruited. Participants without CKD (glomerular filtration rate (eGFR) ≥ 60 mL/min/1,73 m^2 and no proteinuria) were defined as controls, while participants with CKD (eGFR < 60 mL/min/1,73 m^2 and proteinuria) were defined as cases [5]. In this study, we excluded participants with blood transfusions in the previous three months or patients with serum albumin levels of less than three g/dL, haemoglobinopathy, or anaemia from other causes. Eligible participants were invited to participate in the study and conduct interviews. One case was selected per day, corresponding to one control case per day by gender and age. The current laboratory test results and medical history information were collected in the medical records and logbooks of eligible patients and controls. Weight, height, and blood pressure were assessed by qualified staff during medical examinations following standard protocols. The following formula measured body mass index: weight (kg)/[height (m)]^2.

Laboratory measurements

Following the standard procedures, 0.5 mL of venous blood was collected and stored in a tube containing heparin or EDTA anticoagulant. Blood samples were taken following eight hours of fasting and analysed at the University Medical Center at Ho Chi Minh City - Campus 2. Blood HbA1c levels (%) were measured by high-performance liquid chromatography (HPLC) using a Premier Hb9210 (Trinity Biotech, USA). The reference normal ranges for blood HbA1c levels in adults are 4–6%. The blood counts were measured using Cell-Dyn Sapphire (Abbott Diagnostic, USA). Blood fructosamine levels (μmol/L) were measured by

the NBT colorimetric method using an AU680 with reagents from BioSystems (Biosystem, Barcelona, Spain). The reference normal ranges for blood fructosamine levels in adults are 205–285 μmol/L. Fasting blood glucose levels (mg/dL), albumin (g/L), and creatinine (μmol/L) were analysed using the NBT Colorimetric Methode using an AU680 with reagents from BioSystems (Beckman Coulter Ireland Inc, Ireland). The reference normal ranges for glucose, albumin, and creatinine in adults are 70–115 mg/dl, 30–48 g/l, males: 62–106 μmol/L; females: 44–88 μmol/L, respectively.

Data analysis

The baseline characteristics of individuals are reported as frequencies and proportions for categorical variables; for continuous variables, the baseline characteristics are presented as the means and standard deviations or medians and interquartile ranges. Student's t test and the nonparametric Mann–Whitney U test were used to compare the differences between the two groups for normally distributed and nonnormally distributed continuous variables, respectively. The chi-square test was used to compare differences for categorical variables.

The Pearson and Spearman correlation coefficients were used to evaluate the correlation between continuous variables for parametric and nonparametric testing. Receiver operating characteristic (ROC) analysis was employed to compare discriminating abilities and identify the best cut-off value. The cut-off values for sensitivity and specificity were computed using the maximized Youden index. A nonparametric test was used to compare the areas under the ROC curves (AUCs) [24]. Furthermore, Youden's index was applied to identify the cut-off for fructosamine and HbA1c linked with complications. The cut-off for HbA1c was examined at 6.05% and compared with fructosamine as a complication prediction. In two-sided statistical tests, P values of less than 0.05 were considered statistically significant. The statistical analysis was performed using STATA software (version 1.0; StataCorp, TX, USA).

Results

Characteristics of participants

This study included 50 T2DM patients with CKD, 50 T2DM controls without CKD, and 30 healthy subjects. There was no significant difference between the two groups of T2DM patients with and without CKD in terms of sex ($p = 0.198$) or other parameters, including BMI ($p = 0.244$), DBP ($p = 0.423$), albumin ($p = 0.112$), fasting blood glucose ($p = 0.672$), HbA1c ($p = 0.309$), and fructosamine ($p = 0.812$). However, T2DM patients with CKD showed higher serum creatinine levels ($p < 0.001$), SBP ($p < 0.001$), and age ($p = 0.006$) and lower eGFR ($p < 0.001$), haemoglobin ($p < 0.001$), RBC ($p < 0.001$), and Hct ($p < 0.001$) than the T2DM control group. Demographic characteristics and haematological and other parameters between groups are depicted in Table 1.

Table 1
Demographic characteristics and related parameters between the two groups of T2DM patients with and without chronic kidney disease.

Parameters	Healthy subject (1) (n = 30)	T2DM controls (2) (n = 50)	T2DM + CKD cases (3) (n = 50)	p_{12}	p_{13}	p_{23}	p_{123}
Age (Years)	46 ± 10	62 ± 10	68 ± 11	< 0.001	< 0.001	0.006[a]	< 0.001
Males, n (%)	15 (50.0)	19 (38.0)	13 (26.0)	0.293	0.029	0.198[c]	0.091
Females, n (%)	15 (50.0)	31 (62.0)	37 (74.0)				
BMI (kg/m^2)	18.2 (18.0-18.8)	17.9 (17.0–19.0)	18.2 (17.3–20.2)	0.340	0.921	0.244[b]	0.446
SBP (mmHg)	118 ± 10	126 ± 14	141 ± 23	0.007	< 0.001	< 0.001[a]	< 0.001
DBP (mmHg)	75 ± 7	79 ± 11	81 ± 13	0.130	0.018	0.423[a]	0.110
eGFR ($ml/min/1,73m^2$)	99.1 ± 12.8	84.3 ± 15.0	38.8 ± 12.8	< 0.001	< 0.001	< 0.001[a]	< 0.001
Haemoglobin (g/dL)	13.6 ± 1.2	13.6 ± 1.3	12.1 ± 1.7	0.799	< 0.001	< 0,001[a]	< 0.001
Creatinine (mg/dL)	0.9 (0.7–0.9)	0.8 (0.8–0.9)	1.5 (1.2–1.9)	0.687	< 0.001	< 0.001[b]	< 0.001
Albumin (g/dL)	4.3 ± 0.2	4.1 ± 0.3	4.0 ± 0.4	0.809	0.001	0.112[a]	0.001
Fasting blood glucose (mg/dL)	99.5 (96.0-103.0)	136.0 (121.0-180.0)	142.5 (111.0-171.0)	< 0.001	< 0.001	0.672[b]	< 0.001
HbA1c (%)	5.6 (5.5–5.8)	7.4 (6.5–9.5)	7.1 (6.4–8.8)	< 0.001	< 0.001	0.309[b]	< 0.001
Fructosamine (µmol/L)	257.2 (238.1-269.5)	299.0 (275.2–368.0)	310.5 (279.4-340.2)	< 0.001	< 0.001	0.812[b]	< 0.001
RBC ($10^6/mm^3$)	4.6 ± 0.4	4.6 ± 0.5	4.2 ± 0.5	0.809	0.002	< 0,001[a]	0.001

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate; RBC: Red blood cell; Hct: Haematocrit; [a] Student's t test; [b] Mann – Whitney U test; [c] Chi-square test.

Parameters	Healthy subject (1) (n = 30)	T2DM controls (2) (n = 50)	T2DM + CKD cases (3) (n = 50)	p_{12}	p_{13}	p_{23}	p_{123}
Hct (%)	41.4 ± 3.3	41.4 ± 3.7	36.9 ± 6.2	0.947	< 0.001	< 0,001[a]	< 0.001

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate; RBC: Red blood cell; Hct: Haematocrit; [a] Student's t test; [b] Mann – Whitney U test; [c] Chi-square test.

Association of fructosamine level, fructosamine-albumin ratio, and Hb1Ac concentration with related factors in T2DM patients with and without CKD

For HbA1c, there was a positive correlation with fasting blood glucose in T2DM patients with CKD ($r = 0.575$, $p < 0.001$) and an even stronger correlation in those without CKD ($r = 0.758$, $p < 0.001$). In contrast, there was a negative correlation between Hb1Ac and DBP ($r=-0.417$, $p = 0.003$), haemoglobin ($r=-0.316$, $p = 0.026$), and haematocrit ($r=-0.447$, $p = 0.001$). The association was insignificant for other factors. Interestingly, not as expected, we did not identify a significant correlation between fasting blood glucose and fructosamine levels ($r = 0.231$, $p = 0.106$) or the fructosamine-albumin ratio ($r=-0.019$, $p = 0.898$) in T2DM patients with CKD. However, there was a moderate positive correlation between the respective individuals ($r = 0.466$; $p = 0.001$ and $r = 0.436$, $p = 0.002$) in T2DM patients with normal kidney function. In addition, there was no significant relationship between fructosamine level or fructosamine-albumin ratio and the investigated factors (shown in Table 2).

Comparison between the actual fasting blood glucose and the estimated glucose concentration

The estimated glucose concentrations were deduced from fructosamine levels ($eGlucose_{fructosamine}$ = 0.45 x fructosamine + 17.598), fructosamine-albumin ratio ($eGlucose_{fructosamine/albumin}$ = 1.9347 x fructosamine-albumin ratio + 9.517), and Hb1Ac concentrations ($eGlucose_{HbA1c}$ = 29.272 x HbA1c – 75.929) based on corresponding linear regression equations. Table 3 compares the fasting blood glucose and the estimated glucose in T2DM patients at different levels of eGFR. Glucose levels estimated by fructosamine and fructosamine-albumin ratio were not statistically different compared to the actual fasting blood glucose levels in T2DM patients with eGFR less than 45 mL/min/1.73 m^2 ($p = 0.096$) and 30 mL/min/1.73 m^2 ($p = 0.040$), respectively. Meanwhile, glucose levels surmised according to HbA1c were not significantly different from the actual fasting blood glucose levels in patients with different eGFRs.

Table 2
Correlation between fructosamine, fructosamine/albumin, HbA1c, and other parameters in T2DM patients with and without CKD

Parameters	Fructosamine		Fructosamine/Albumin		HbA1c	
	T2DM	T2DM + CKD	T2DM	T2DM + CKD	T2DM	T2DM + CKD
Fasting blood glucose	0.466**	0.231	0.436**	-0.019	0.758**	0.575**
BMI[a]	-0.088	0.118	-0.170	0.153	-0.072	-0.052
SBP	0.185	-0.131	0.095	-0.023	0.165	-0.086
DBP	0.134	-0.184	0.213	-0.193	0.128	-0.417**
eGFR	-0.136	0.188	-0.067	0.102	0.134	-0.162
Haemoglobin	0.014	-0.133	-0.026	-0.080	0.018	-0.316*
Serum creatinine	0.112	-0.057	0.134	-0.005	0.003	0.004
Albumin	0.116	0.269	-0.153	-0.290	-0.040	0.010
RBC	-0.086	-0.154	-0.064	-0.085	0.064	-0.155
Hct	0.009	-0.160	-0.049	-0.093	-0.001	-0.447**
* Correlation coefficient (r) is significant at the 0.05* or 0.01** level (2-tailed)						

Table 3
Actual fasting blood glucose and estimated glucose were calculated based on fructosamine, fructosamine-albumin ratio, and HbA1c in T2DM patients.

eGFR (mL/min/1.73 m^2)	n	Glucose (mg/dL)			
		(1)	(2)	(3)	(4)
≥ 60	50	136.0 (121.0-180.0)	152.1 (141.4-183.2)	140.7 (114.3-202.2)	159.3 (133.3–194.0)
			p = 0.022	p = 0.842	p = 0.041
< 60	50	142.5 (111.0-171.0)	157.3 (143.3-170.7)	133.1 (111.4-181.7)	162.9 (144.0-178.1)
			p = 0.015	p = 0.934	p = 0.004
< 45	32	143.5 (120.5–169.0)	156.2 (140.0-168.3)	155.2 (111.4-187.5)	159.8 (140.9-180.7)
			p = 0.096	p = 0.477	p = 0.040
< 30	10	128.5 (123.0-145.0)	146.2 (138.5–161.0)	127.5 (99.7-158.2)	154.1 (138.5-176.8)
			p = 0.143	p = 0.796	p = 0.123

(1) The actual fasting blood glucose level in T2DM patients; (2) The estimated glucose levels were calculated based on fructosamine; (3) The estimated glucose levels were calculated based on HbA1c; (4) The estimated glucose levels were calculated based on a fructosamine-albumin ratio.

ROC analysis and optimal cut-off for monitoring the response to T2DM treatment

Table 4 and Fig. 1 present the results of ROC analysis and AUC (95% CI) for fasting blood glucose, HbA1c, fructosamine, and fructosamine-albumin ratio in T2DM patients with and without CKD. ROC analysis revealed that these parameters were strong predictors in T2DM patients with and without CKD (AUC > 0.800 and $p < 0.001$). However, their AUCs were different from each other, representing 1.000, 0.848, and 0.815 for HbA1c, fructosamine-albumin ratio, and fructosamine, respectively. The optimal cut-off points for the parameters in monitoring the response to T2DM treatment were determined to be 6%, 67, and 270 µmol/g, respectively. In this study, we used an HbA1c level threshold larger than 6% as a reference to determine the response to diabetes treatment. For fructosamine, we observed a high sensitivity of 83.9% to detect T2DM with a very high negative predictive value (98.7%), even though the positive predictive value was significantly low (15.3%). The overall accuracy was recorded at 73.6%. For the fructosamine-albumin ratio, we also obtained a similar result with a slightly higher specificity (81.1%) and positive predictive value (19.2%) than fructosamine. The overall accuracy was recorded as 80.9% for the fructosamine-albumin ratio (shown in Table 5). According to Fig. 1, we could see that HbA1c had AUC decreased in T2DM patients with CKD (0.966 vs. 1.000), while AUCs of fructosamine (0.867 vs. 0.815)

and fructosamine-albumin ratio (0.923 vs. 0.848) increased in this group. Even though the patient population did not have abnormal albumin levels (p = 0.112; shown in Table 2), we postulated that the AUC values would be better for anomalous albumin concentrations.

Table 4
The AUC of fasting blood glucose, HbA1c, fructosamine, and fructosamine-albumin ratio in T2DM patients with and without CKD.

Parameters	T2DM			T2DM + CKD			Cut-off	Youden's index
	AUC	95% IC	p	AUC	95% CI	p		
Fasting blood glucose	0.933 ± 0.033	0.869–0.997	< 0.001	0.901 ± 0.036	0.830–0.972	< 0.001	108	0.807
HbA1c	1.000 ± 0.000	1.000–1.000	< 0.001	0.966 ± 0.020	0.927-1.000	< 0.001	6	0.880
Fructosamine	0.815 ± 0.047	0.722–0.908	< 0.001	0.867 ± 0.040	0.798–0.945	< 0.001	270	0.587
Fructosamine/Albumin	0.848 ± 0.042	0.766–0.930	< 0.001	0.923 ± 0.029	0.866–0.980	< 0.001	67	0.720

AUC: area under the curve; Fasting blood glucose (mg/dL); HbA1c (%); Fructosamine (µmol/L)

Table 5
Value of fructosamine and fructosamine-albumin ratio in monitoring the response to T2DM treatment

Parameters		HbA1c (%)		Sen	Spe	PPV	NPV	Acc
		+	-					
Fructosamine	+	78	10	83.9	73.0	15.3	98.7	73.6
	-	15	27					
Fructosamine-Albumin ratio	+	72	7	77.4	81.1	19.2	98.4	80.9
	-	21	30					

The disease prevalence is considered to be 5.5%; Sen: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value; Acc: accuracy; Cut-off points for HbA1c, fructosamine, and fructosamine/albumin were 6%, 270 (µmol/L) and 67, respectively.

Discussion

HbA1c has been used to track blood glucose concentrations for type 2 diabetic patients with normal kidney function [17]. Even though there is a good association between HbA1c and blood glucose levels,

calculating estimated blood glucose from HbA1c may be controversial in patients with late-stage CKD. Chen *et al.* provided evidence that in these patients, calculated blood glucose from HbA1c concentrations was more subordinate than assumed for the same glucose concentration in patients without abnormal kidney function [17]. While HbA1c is used as a standard biomarker for long-term glycaemic control in T2DM patients without nephropathy, this indicator substantially underestimates glycaemic control in T2DM patients with CKD stages 4 and 5 (eGFR < 30 mL/min/1.73 m^2) [4, 5, 25]. The reason is that the short lifespan of haemoglobin results from the anaemia condition or erythropoietin treatment [26]. Speeckaert *et al.* suggested that the relationship between HbA1c and blood glucose concentration varies as the eGFR declines [8]. Whereas George *et al.* found that fasting blood glucose correlated most closely with HbA1c compared to the substitute markers of chronic glycaemia, the association differed by CKD status [5].

Nonetheless, our data showed that HbA1c levels were strongly correlated with the estimated blood glucose levels in T2DM patients at any level of observed eGFR (shown in Table 3). This finding also concurred with and supported previous studies [6, 17]. Consequently, HbA1c reflected the correct glycaemic control in the T2DM Vietnamese patient population with and without CKD. In this study, we did not recognize any effects of the reduced red blood cells on T2DM patients with CKD, even though approximately 10% of the patients were treated with erythropoietin (data not shown). The treatment might alter the reflection of HbA1c in these patients but cannot be identified by the study.

The current study investigated whether the fructosamine level or fructosamine-albumin ratio could be used as a reliable glycaemic control indicator in T2DM patients with CKD, in which HbA1c might be unsuitable in cases of decreased red blood cell mass and survival and iron deficiency anaemia. The fructosamine levels and fructosamine-albumin ratio were correlated with fasting blood glucose levels in T2DM patients without CKD ($r = 0.466$ and $r = 0.436$, respectively). In contrast, the correlation between HbA1c levels and blood glucose levels was even more potent ($r = 0.758$) in this group and the group with CKD ($r = 0.575$). Our results support a close relationship between HbA1c and blood glucose concentrations for type 2 diabetic patients with both standard and abnormal kidney function [17]. Moreover, estimated glucose from HbA1c levels showed significant similarity to actual fasting blood glucose concentrations at all eGFR levels ($p > 0.05$). Meanwhile, as previously stated, there was no statistically significant difference between calculated blood glucose levels based on fructosamine levels or fructosamine-albumin ratio and actual blood glucose concentrations in T2DM patients with eGFR less than 45 and 30 mL/min/1.73 m^2, respectively. Because of these eGFR levels, the estimated glucose calculated from fructosamine levels and fructosamine-albumin ratio in the present study was higher than the mean blood glucose level. Therefore, assessing glycaemic control based on fructosamine levels and the fructosamine-albumin ratio may be problematic. Our findings did not agree with those of a previous study carried out by Chen *et al.* [17]. The study showed that fructosamine tended to be equivalent between the two groups of patients with normal kidney function versus patients with CKD (eGFR = 15–60 mL/min/1.73 m^2) after being corrected for serum albumin concentration. It is well known that fructosamine is not affected by low haemoglobin levels in T2DM patients with CKD and the high levels of

urea in their blood; however, it is highly dependent on serum albumin [17, 27]. In our study, T2DM patients with CKD had similar albumin concentrations (4.0 vs. 4.1) compared to the control group and were in the normal range of 3.8–5.1 g/dL. To eliminate the effect of protein turnover, the fructosamine assay was corrected for albumin concentration by the fructosamine-albumin ratio despite albumin's normal range in our study. The fructosamine-albumin ratio was explicitly presented as an alternative way of assessing glucose levels in the population with an eGFR less than 30 mL/min/1.73 m^2. Values of fructosamine-albumin ratio in refecting glycaemic control were better than individual fructosamine levels in terms of larger AUC (0.923 vs. 0.867) in T2DM patients with CKD. In addition, the specificity, PPV, and accuracy of the ratio were improved despite slightly decreased sensitivity (shown in Table 5).

We estimated the cut-off point of fructosamine at 270 μmol/L based on the cut-off level of HbA1c > 6.0%. Thus, our study suggests the cut-off value of fructosamine for glycaemic control monitoring in T2DM Vietnamese patients with and without CKD. Our cut-off finding was similar to that of a previous study, which found the ideal fructosamine cut-off level to be 293 μmol/L. In a prospective study, this high level of fructosamine cut-off linked the patients with complications of 11.2-fold more likely to develop a prosthetic joint infection [28].

To the best of our knowledge, this is the first case–control study to identify the correlation between fructosamine concentrations, fructosamine-albumin ratio or HbA1c levels, and blood glucose levels in T2DM patients with CKD in the Vietnamese population. However, our study has several limitations. First, the small sample size may prevent us from proving that the fructosamine or fructosamine-albumin ratio is better than HbA1c in T2DM patients with CKD. Second, we did not have a chance to assess fasting blood glucose by the continuous glucose monitoring method, which is usually considered a reference method in this situation [6, 9]. Third, we did not concurrently evaluate another parameter, such as glycated albumin through fructosamine, which is a measure of glycated serum protein, including glycated albumin. Despite the drawbacks mentioned above, the findings of our study suggest that the HbA1 indicator is still a standard parameter of glycaemic control in T2DM patients with and without CKD. Meanwhile, fructosamine and fructosamine-albumin ratios were alternative biomarkers for short-term glycaemic control in T2DM patients with CKD.

Conclusions

Overall, the present study comprehensively identifies the correlations between the fructosamine or fructosamine-albumin ratio and fasting blood glucose levels among T2DM patients with CKD (eGFR levels lower than 45 and 30 mL/min/1.73 m^2, respectively) and can be a reliable, affordable, and fast indicator replacement for HbA1c to reflect glycaemic control in these patients. Our findings contribute to the fundamental recommendations for monitoring glycaemic control in Vietnamese patients. Future prospective research is warranted to confirm our results and investigate the correlation between fructosamine or fructosamine-albumin ratio and blood glucose levels in cases of low albumin levels.

Declarations

Statement of Ethics

This study protocol was reviewed and approved by the ethics committees at the University of Medicine and Pharmacy at Ho Chi Minh City (reference number: 640/HĐĐĐ-ĐHYD, signed on 29/09/2020). All participants provided written informed consent before the investigations. This work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for Experiments in Humans.

Data Availability Statement

The data and supportive information are available within the article.

Conflict of Interest Statement

The authors declare no conflict of interest, financial or otherwise.

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Not applicable

Author Contributions

TMH designed the experiment. TTD collected specimens and performed clinical diagnoses. TMH, TTD, and ATN performed data analysis. TMH produced the first draft. ATN edited the manuscripts critically. All the authors have read and approved the final version of the manuscripts.

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Figures

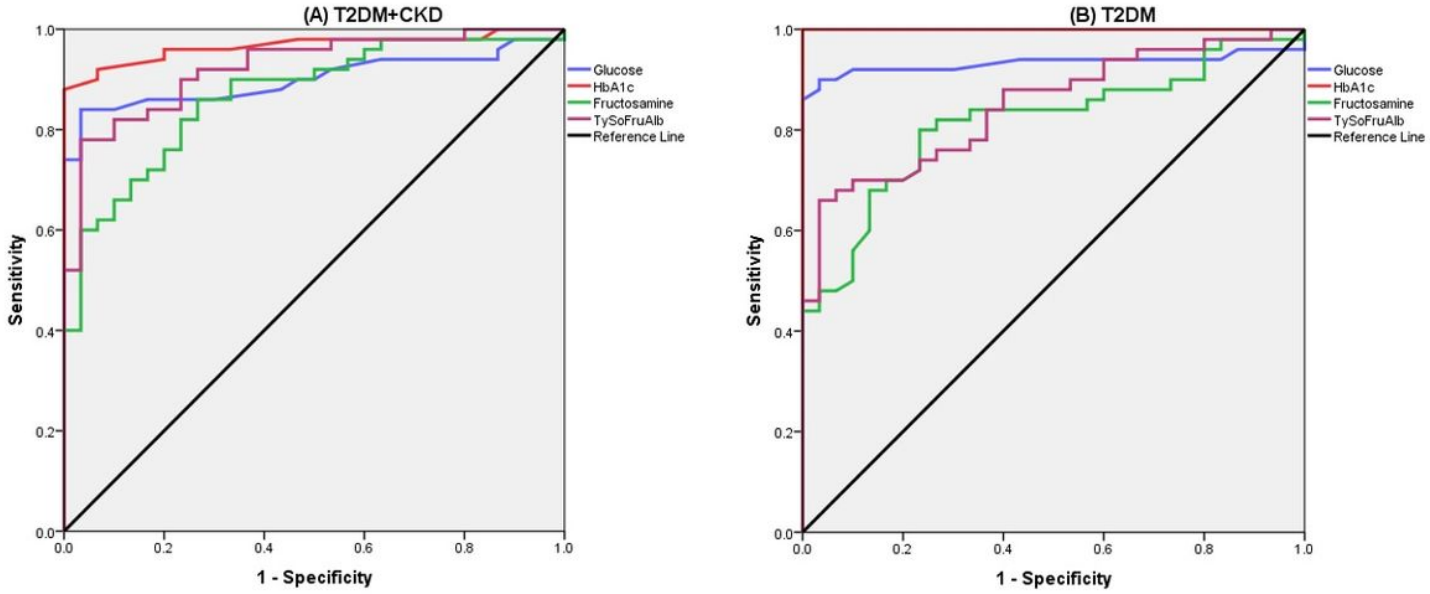

Figure 1

The ROC curve compares the fructosamine concentrations, fructosamine-albumin ratio, and HbA1c levels in reflecting glycaemic control among type 2 diabetes mellitus patients with (A) or without (B) chronic kidney disease.