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RESEARCH

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The utility of estimation of glomerular filtration rate by serum cystatin C as a predictor of diabetic kidney disease in both type I and type II diabetic patients: a single center study

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Abstract

Background Diabetic kidney disease is a major microvascular complication of diabetes mellitus and is the leading cause of end-stage renal disease all over the world. The general recommendation for the subjects with DM is to perform kidney function as screening: in T1DM, 5 years after diagnosis, and in type 2, at the time of diagnosis. The early diagnosis of diabetic kidney disease depends on the albumin excretion ratio; however, the albumin excretion ratio (AER) does not correlate with the severity and progression of the disease.

Methods The subjects in this study included thirty patients with type 1 diabetes mellitus and thirty patients with type 2 diabetes mellitus who were recruited from the outpatient clinic and inpatient in the Internal Medicine Department at Benha University Hospitals in the endocrinology unit from January 2022 to January 2023 as cases who were subground according to albuminuria into two groups (normoalbuminuria less than 30 mg/24 h urinary collection) and albuminuric group more than 30 mg/24 h urinary collection; all patients were subjected to thorough history including baseline characteristics, examination, and related laboratory investigations.

Results Serum cystatin C level at a cutoff value of 82 was associated with sensitivity (81.4) and specificity (82.4), and it was negatively significantly correlated with BMI, duration of diabetes mellitus, albuminuria, blood urea, and serum creatinine, and it was positively significantly correlated with e-GFR creatinine.

Conclusion Serum cystatin C can be used as an early marker of diabetic kidney disease in both type I and type II diabetic patients better than AER and serum creatinine.

Keywords Cystatin C, Predictor, Diabetic kidney disease

Introduction

Both type 1 diabetes and type 2 diabetes can be complicated by several microvascular complications including retinopathy, neuropathy, and nephropathy which is the leading cause of the need for renal replacement therapy either hemodialysis or transplantation [1]. Thirty to 40% of patients with diabetes mellitus develop diabetic kidney disease, and the underlying pathogenesis is

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multifactorial including metabolic, inflammatory, and hemodynamic pathways [2].

Diabetes mellitus (T2DM) is characterized by chronic hyperglycemia either due to inadequate insulin secretion or insulin resistance leading to the activation of metabolic pathways and endothelial dysfunction together with fibrotic and inflammatory pathways; also, there is lipotoxicity leading to increase cardiovascular disease, nephropathy, and retinopathy.

These complications impair the quality of life in T2DM patients, while the development of nephropathy in T1DM follows the same pathways as T2DM, but its course is more protracted and needs a longer duration to develop [3].

Over the past century, there were different measuring methods for the assessment of renal function including serum creatinine, glomerular filtration rate (GFR), blood urea, and serum cystatin C [4].

Evaluating the measured GFR (mGFR) requires measurement of serum creatinine which is an endogenous marker, or using an exogenous marker such as inulin and assessment of serum creatinine and serum cystatin C are considered as rapid tests for assessing renal function [4].

The UK's National Institute for Health and Care Excellence (NICE) guideline for the Assessment and management of CKD in adults stated that serum cystatin C for the estimation of GFR is more accurate than serum creatinine for determining the disease outcomes and may reduce the overall burden of CKD [5]. Cystatin C (Cys C), with a molecular weight of 13,343 Da, is a competitive extracellular inhibitor of cysteine proteinases that can be steadily produced and constitutively secreted by all nucleated cells and mainly controls extracellular protease activity [5]. It has been shown that Cys C can modulate lysosomal protein turnover after cellular internalization via endocytosis, thereby indicating the role of Cys C in modulating target tissue homeostasis after cellular reuptake in vivo. Moreover, Cys C also contributes to endothelial cell and tubule formation and shows angiogenic characteristics in vitro [6]. Cystatin C is filtered by the kidneys through glomerular filtration and is completely reabsorbed in the distal tubule without tubular secretion [7] in contrast to serum creatinine which is susceptible to modifications by external factors such as age, diet, and body mass. Serum Cys C is considered more specific than serum creatinine in assessing renal function and improving the estimation of glomerular filtration rate (GFR) when compared to the methods based on creatinine alone [8]. Different studies have shown that Cys C could be an independent risk factor for the development of cardiovascular disease as coronary heart disease or congestive heart failure [9].

- Serum Cys C is more accurate than serum creatinine as it is not affected by muscle mass. The circulating level of serum Cys C is affected by different conditions such as thyroid disorders, obesity, inflammation, cigarette smoking, viral load in HIV-infected patients, or high-dose steroid therapy. Cys C can be measured by nephelometric or turbid metric assays, but standardization has been needed. Standardization using certified reference material for Cys C measurement improves the utility of this marker [10].
- Several studies suggested that cystatin C might predict the risk of developing CKD, in the preclinical stage, so it is considered as an early predictor. Also, serum cystatin C rises with the advancing of age, so it could be used as a marker of adverse age-related health outcomes, including all-cause mortality, death from cardiovascular disease, multimorbidity, and declining physical and cognitive function [11].
- Chronic kidney disease is defined as a functional or structural abnormality that persists for more than 3 months or is defined as albuminuria (UACRi $\geq$ 30 mg/g) and/or reduced kidney function (e-GFR $<$ 60 ml/min/1.73 m^2) present for $>$ 3 months in the absence of signs or symptoms of other primary causes of kidney damage. So, albuminuria and reduced GFR are considered independent risk factors for CKD progression and cardiovascular morbidity and mortality [12].

Subject and methods

This is a cross-sectional study that was carried out on 60 patients: 30 known to have type 2 diabetes and 30 patients with type 1 diabetes; the study was conducted on males and females who were attending the outpatient clinic and inpatient of the Internal Medicine Department at Benha University Hospitals. Diabetic patients were classified into two groups: diabetes type 1 and type 2 with the presence of albuminuria and normoalbuminuria. Diagnosis of diabetes was done according to the American diabetes association (ADA) 2022 [13].

We used two methods: for the assessment of serum creatinine (e-GFR creat) and serum cystatin C (e-GFR cys) and for the estimation of glomerular filtration for all participants. For e-GFR creat and e-GFR cys, equations from the Chronic Kidney Disease Epidemiology Collaboration were used [13].

The presence of albuminuria was done by assessment of 24 h urinary albumin excretion (mg/day). The following patients were excluded including pregnant females with diabetes and thyroid disorders and patients on steroids; recent infection or inflammation, cigarette smoking, HIV-infected patients, and also other causes of false proteinuria in diabetic patients were excluded as the presence of fever, urinary tract infection, hematuria, and heart failure also patients presented with rapidly increasing albuminuria or nephrotic syndrome, rapidly decreasing e-GFR, active urinary sediment (e.g., cellular casts in urine), the absence of diabetic retinopathy in patients with type 1 diabetes or signs or symptoms of collagen vascular disease they were excluded and referred to renal biopsy. Fundus examinations were done on all patients, and diabetic kidney disease (DKD) is defined by albuminuria (increased urinary albumin excretion is defined as ≥ 30 mg/g) and progressive reduction in estimated glomerular filtration rate (e-GFR) in the setting of a long duration of diabetes (> 10-year duration of type 1 diabetes; may be present at diagnosis in type 2 diabetes) and is typically associated with retinopathy. In most patients with diabetes, chronic kidney disease (CKD) can be attributable to diabetes if these features are met; however, CKD may be present without retinopathy in type 2 diabetes, and without albuminuria in type 1 and type 2 diabetes, and according to the staging of diabetic kidney disease, stages I and II are normoalbuminuric, and as there was a possibility that the main affection of diabetes on the kidney could involve the tubule interstitial and vascular component without glomerular affection, we further sub-classified the studied groups into the normoalbuminuria group and albuminuria group. A written consent was taken from all patients before starting the study. Assessment of the patients included demographic factors such as age, sex, body mass index (BMI), and clinical assessments which included type and duration of diabetes and control of diabetes. Laboratory tests are in the form of fasting blood glucose, HBA1C, serum creatinine, blood urea, serum cystatin, estimated GFR-based creatinine, and estimated GFR-based cystatin C.

Normoalbuminuric DKD is defined as normal or high GFR with no albuminuria including stage I and II diabetic nephropathy.

Microaluminuric DKD is defined as mostly incipient stage III in which albuminuria was 30 to 300 mg/day.

Macroalbuminuric DKD is defined as there is a decrease of GFR and albuminuria was more than 300 mg/day.

Normal serum cystatin level is 0.62–1.15 mg/l.

The CKD-EPI (creatinine-based) equation, expressed as a single equation, is:

$$\mathrm{GFR} = 141 * \min(\mathrm{Scr}/\kappa, 1)\alpha * \max(\mathrm{Scr}/\kappa, 1) - 1.209 * 0.993\ \mathrm{Age} * 1.018\ [\text{if female}] * 1.159\ [\text{if black}]$$

Scr is serum creatinine (mg/dl), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1, and max means the maximum of Scr/κ or 1.

CKD-EPI creatinine-cystatin equation (2021):

$$\mathrm{e-GFRcr-cys} = 135 \times \min(\mathrm{Scr}/\kappa 1)\alpha \times \max(\mathrm{Scr}/\kappa 1) - 0.544 \times \min(\mathrm{Scys}/0.8, 1) - 0.323 \times \max(\mathrm{Scys}/0.8, 1) - 0.778 \times 0.9961\ \mathrm{Age} \times 0.963\ [\text{if female}]$$

where Scr is the standardized serum creatinine in mg/dl

$\kappa = 0.7$ (females) or 0.9 (males); $\alpha = -0.219$ (female) or -0.144 (male)

min(Scr/κ, 1) is the minimum of Scr/κ or 1.0 max(Scr/κ,1) is the maximum of Scr/κ or 1.0 Scys is the standardized serum cystatin C in mg/l.

Age (years)

Statistical analysis

The SPSS version 26 software was used for the analysis of the collected data (Spss Inc., Chicago, ILL Company). Categorical data were presented as numbers and percentages while quantitative data were expressed as mean ± standard deviation. Inter-group comparison of categorical data was performed by using the chi-square test (X^2 value), and the Pearson correlation coefficient (r) test was used to correlate different parameters. The sensitivity and specificity were examined using ROC curve analysis to determine the best cutoff point as well as the diagnostic power of the test (Fig. 1). Logistic regression analysis was used to determine which of these factors is considered a significant predictor. P value < 0.05 was considered statistically significant.

Results

The age of the studied groups ranges from 36.5 ± 14.7 years of which 38 patients were (63.3%) males, 22 (36.7%) were female (71.7), and mean and standard deviation of BMI was 28 ± 9.6 (Table 1).

Eighty percent of type 2 diabetic patients had proteinuria > 30 mg/day and 63.3% of type 1 diabetic patients had proteinuria > 30 vs 20.0% of type II diabetic patients who had proteinuria < 30 mg/day and 36.7% of type I diabetic patients who had proteinuria < 30 mg/day (Table 2).

Regarding FBG ratio and HBA1C, we found a highly significant difference between the studied participants.

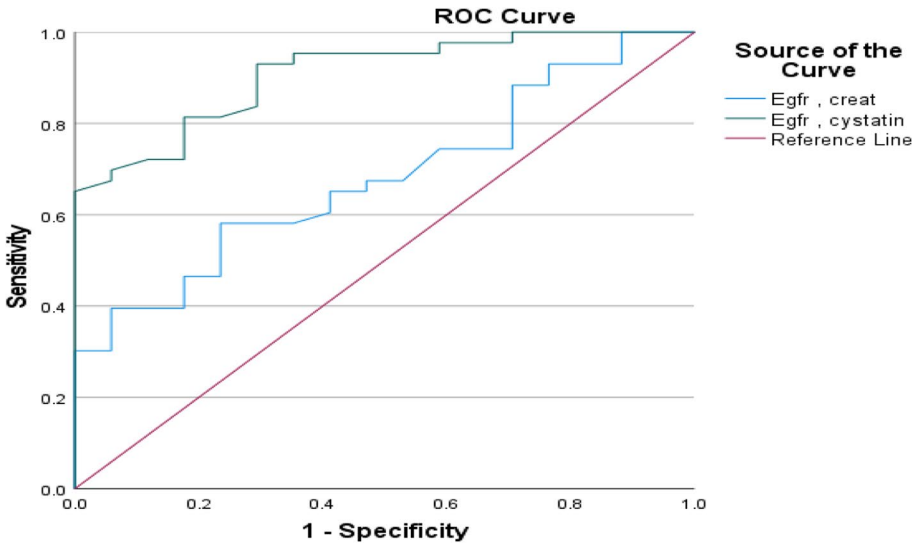

Fig. 1 ROC curve for evaluation of e-GFRcreat and e-GFRcys

Table 1 Demographic data of the studied groups

Age (mean ± SD)		**36.5 ± 14.7**
Sex, no. (%)	Female	22 (36.7)
	Male	38 (63.3)
DM, no. (%)	Type 1	30 (50.0)
	Type 2	30 (50.0)
Albuminuria, no. (%)	< 30	17 (28.3)
	> 30	43 (71.7)
BMI (mean ± SD)		28 ± 9.6

The macroalbuminuric group of patients (A3) showed the highest values of HbA1c than other groups, and there was a highly significant difference between the groups found (Table 3).

As regard the DM duration, there was highly significant differences between the studied groups (Table 4). e-GFR cystatin was negatively significantly correlated with BMI, duration of diabetes, albuminuria, blood urea, and serum creatinine and significantly positive correlation with e-GFR creatinine (Table 4).

The majority of normoalbuminuric patients had normal e-GFR-based creatinine values (0.93–0.98 mg/dl). This subset was "creatinine blind" but had increased levels of serum cystatin C and decreased e-GFR-based cystatin C levels.

The macroalbuminuric group (A3) showed the highest mean of serum cystatin C (mean = 2.39), and this was statistically significant when compared with A2 and A1 (Table 5). Comparison between normoalbuminuria with GFR ≥ 90 and serum cystatin C was found to be statistically significant (Tables 6, 7, 8, and 9). Serum cystatin C level at a cutoff value of 82 was associated with sensitivity of 81.4 and specificity of 82.4 (Table 10). Serum cystatin C and e-GFR were negatively correlated, while serum cystatin C was positively correlated with creatinine, albuminuria, HbA1c, FBG, and DM duration. A non-significant correlation between serum cystatin C and BUN, age, and BMI was found (Table 11).

Linear regression analysis was done and revealed that serum cystatin C can be considered as a predictor for glomerular filtration rate (Table 12).

Table 2 Comparison between T1DM and T2DM regarding albuminuria

		Type 1		**Type 2**		***P*-value**
		No.	**%**	**No.**	**%**	
Albuminuria	< 30 mg/24 h	11	36.7%	6	20.0%	0.2
	> 30mg/24 h	19	63.3%	24	80.0%	
Total		30	100.0%	30	100.0%	

Table 3 Comparison between the degree of albuminuria and the parameters of glycemic control in the studied groups

Variable	(A1) Normoalbuminuria group			(A2) Microalbuminuria group			(A3) Macroalbuminuria group			ANOVA	*P*
	Mean	± SD	Range	Mean	± SD	Range	Mean	± SD	Range		
FBS (mg/dl)	157.0	22.3	120–199	192.6	51.2	125–275	198.8	41.5	136–260	**20.6**	**< 0.001(HS)**
HbA1c (%)	7.6	1.13	5.8–9.0	9.1	1.46	6.2–12.0	9.8	1.85	7.5–13.2	**29.0**	**< 0.001(HS)**
Bonferroni test for significant pairs											
Pairs				***P* (FBS)**				***P* (HbA1c)**			
A1 vs A2				0.15				0.06			
A1 vs A3				0.058				0.003			
A2 vs A3				0.99				0.98			

Table 4 Correlation between the duration of DM and the degree of albuminuria between the studied groups

Group	Duration of DM (years)			ANOVA	*P*	Bonferroni test for sig. pairs	*P*
	Mean	± SD	Range				
Normoalbuminuria (A1)	3.9	1.59	1–6	28.8	< 0.001 (HS)	A1 vs A2	< 0.001
Microalbuminuria (A2)	9.9	3.10	6–15			A1 vs A3	< 0.001
Macroalbuminuria (A3)	14.4	4.37	7–20			A2 vs A3	0.003

Table 5 Comparison between the studied groups regarding serum cystatin C

Group	Serum cystatin			KWT	*P*
	Mean	± SD	Range		
A1	0.89	0.18	0.64–1.18		
A2	1.37	0.54	0.67–2.9		
A3	2.39	0.46	1.24–3.24		

Table 6 Post hoc multiple comparisons for the significant pairs

Bonferroni-adjusted Mann-Whitney test for significant pairs of cystatin	
Pairs	***P* (0.008)**
A1 vs A2	0.038
A1 vs A3	< 0.001
A2 vs A3	< 0.001

Table 7 Mean of cystatin C in the normoalbuminuria group with e-GFR > 90

Group	Serum cystatin			MWU	*P*
	Mean	± SD	Range		
Normoalbuminuria (A1) with GFR ≥ 90	0.92	0.14	0.64–0.99		

Discussion

Diabetic kidney disease may be present at the time of diagnosis of type 2 diabetes (T2D) while inpatients with type 1 diabetes, a more protracted course of up to 10 years, could elapse before the development of CKD [14].

The pathology of diabetic nephropathy (DN) could involve the glomular, vascular, and tubule-interstitial tissues of the kidneys as it affects the integrity of the filtration barrier and with extensive glomerular and tubule-interstitial fibrosis together with the affection of glomerular capillaries and renal arteries [15].

Different guidelines recommended estimation of glomerular filtration rate (e-GFR), calculated using the CKD Epidemiology Collaboration (CKD-EPI), and assessment of albuminuria should be measured using urine albumin-to-creatinine ratio (UACR) [16].

In the preclinical state, estimation of GFR is considered the most accurate measurement of kidney disease and is affected before the appearance of clinical symptoms; there were different methods available for assessment of GFR [17].

Our study showed that serum cystatin is not affected by age which is matching with (Fried et al. and Filler et al.) who stated that age did not affect serum cystatin levels; also, this was in line with Porto et al. who stated that cystatin C levels were less dependent on age, gender, ethnicity, diet, and muscle mass compared to creatinine and that cystatin C is equal or superior to the other available biomarkers in a wide range of different patient populations, including diabetic patients. In chronic kidney disease

Table 8 Stepwise multiple linear regression analysis for the predictors of GFR among the studied patients

	R^2		Adjusted R^2	SEE	*F*	*P*-value
Model summary	0.432		0.401	14.7	14.07	< 0.001 (HS)
Variable	**Unstandardized coefficients**		**Standardized coefficients**	**95% CI of *B***	***T***	***P***
	B	**Std. error**	**Beta**			
(Constant)	139.8	12.7		114.1 to 165.6	11.0	< 0.001 (HS)
HbA1c	−4.36	1.69	−0.401	−6.79 to −0.93	2.57	0.014 (S)
Serum Cystatin C	−8.28	3.87	−0.333	−16.1 to −0.432	2.14	0.039 (S)

eGFR = 139.8 − 4.36 (Hb1A1c) − 8.28 (serum cystatin C)

Table 9 Area under the curve

Test result variable(s)	Area	*P*-value	95% confidence interval	
			Lower bound	Upper bound
e-GFRcreat (CKD-epi)	0.681	0.03	0.54	0.82
e-GFR cystatin (CKD-epi)	0.908	< 0.001	0.83	0.98

Table 10 Cutoff value for e-GFR cys

	Cutoff	Sensitivity	Specificity
e-GFR cystatin (CKD-epi)	82	81.4	82.4

Table 11 Correlation between e-GFR cystatin and different variables

	r	*P*-value
Age	−0.29	0.008
BMI	−0.47	< 0.001
Duration of diabetes	−0.64	< 0.001
Albuminuria	−0.63	< 0.001
HA1C	−0.43	< 0.001
Blood urea	−0.48	< 0.001
Serum creatinine	−0.43	< 0.001
e-GFR creat	0.45	< 0.001

Table 12 Logistic regression analysis for prediction of albuminuria from e-GFR and cystatin

	Wald	*B*	95% CI	*P*-value
e-GFR cys	13.6	0.95	0.93–0.98	< 0.001

(CKD), and after kidney transplant, this was not concordant with Christenson et al. [18] who found a significant positive correlation between serum cystatin and age.

Both muscle mass and GFR decrease with the advancement of age which made the measurement of serum creatinine less useful in identifying a decrease in GFR in elderly people [19].

The production of cystatin C is not strongly affected by muscle mass so cystatin C will increase due to the decrease of GFR with age. Cystatin C is more useful than creatinine to demonstrate the decrease in GFR in the elderly [20].

Cystatin C is produced at a constant rate by most nucleated, and this rate may be affected by aging, apoptosis, and cell damage [21]. Regarding gender, in our study, cystatin C was not affected by gender; this finding was also reported by Uhlmann et al. [21] who stated that there was no significant difference in males and females.

Regarding the cystatin C level, Akdyhsei–Andersen et al. [22] reported the same results, but Knight et al. [23] stated that serum cystatin is affected by gender, liver diseases, and infection. Piwowar et al. [24] found cystatin was slightly higher in males and related to age, while Finney et al. [25] reported that cystatin lower in women than in men. The explanation for this finding is that the production of cystatin C undergoes higher extra renal elimination and different hormonal variations which could account for the difference by gender [26].

Owing to the low molecular weight and positive charge of cystatin C, it is easily filtered, and its serum concentration is independent of gender, so it is not a confounder in assessing glomerular filtration rate [27].

This controversy may be because cystatin C strongly correlates with central obesity parameters and is much better used as a predictor of metabolic syndrome; adipocytes can produce and secret several proteins including cystatin as the cystatin level is twice higher in subcutaneous tissue and adipose than in non-adipose tissue. Cystatin level was found to be elevated in obesity [28, 29].

In our study, we found that there was a positive correlation between HBA1C and cystatin level, and this was

concordant with Lee et al. who found that cystatin C level rises in metabolic syndrome, and it was associated with insulin resistance, hyperglycemia, and endothelial dysfunction [30].

Also, in the study done by Lee et al., they found that insulin resistance and inflammation may have an additional role in the link between cystatin C and cardiovascular disease in type 2 diabetes mellitus patients.

Also, this was in line with Uruska et al. who stated that there was an association with insulin resistance also detected in type 1 diabetes mellitus and not only in type 2 diabetes mellitus [31].

In contrast to our study, Tian et al. [32] reported a non-significant correlation between cystatin level and blood glucose level. Different confounders affect the reference values of serum cystatin C such as age, sex, and ethnicity. In different studies, the mean reference interval was between 0.52 and 0.98 mg/l. For women, the average reference interval is 0.52 to 0.90 mg/l with a mean of 0.71 mg/l. For men, the average reference interval is 0.56 to 0.98 mg/l with a mean of 0.77 mg/l. The normal values decrease until the first year of life, remaining relatively stable before they increase again especially beyond the age of 50. Creatinine levels increase until puberty and differ according to gender, making their interpretation problematic for pediatric patients as reported by Kristensen et al. [33].

In a study done by Donahue et al., they found that there was an association between cystatin C and the development of type 2 diabetes mellitus, and several studies have been done to prove the link between cystatin C and type 2 diabetes mellitus [34].

In our study, we found that the association between cystatin C and HBA1c was concordant with a study done by the Western New York Health which showed an approximately threefold increased risk of progression to pre-diabetes among those in the highest quintile of cystatin C in a population free of diabetes and known CVD. Also, this was in line with a population-based study done by Sahakyan et al. [35] who stated the association of serum cystatin C with the incidence of type 2 diabetes mellitus over a 15-year follow-up period.

The incidence of diabetes was estimated to be 9.6%. However, the association did not remain significant after adjustment for glycosylated hemoglobin (HbA1c). Our study showed a significant negative correlation between e-GFR-based cystatin and different variables such as age, BMI, duration of diabetes, albuminuria, and blood urea.

This was concordant with Harmoinen et al. [36] and Xia et al. [37] who found that serum cystatin was more sensitive to assess GFR in type2 diabetes patients than serum creatinine.

In contrast with our study, Oddoze et al. [38] found that serum creatinine was better than serum cystatin C for estimation of GFR in diabetic patients. The controversies about serum cystatin effectiveness as reported by Knight et al. is that there were many factors associated with serum cystatin level such as smoking, CRP, gender, age, and weight. Lamb and Stowe reported that serum cystatin may be affected by rheumatoid factors and high dose of glucocorticoids.

In our study, we excluded thyroid disease but Manett et al. [39] found that serum cystatin was affected in impaired thyroid functions even in a mild form. Although in our study we did not assess the cardiovascular morbidity in the recruited patients, in a study done by Beilby et al., they found that blood levels of cystatin C might rise sooner than creatinine, and this was concordant with our results; however, several reports also indicate that cystatin C is better than creatinine for predicting risk in cardiovascular disease, although other studies did not conclude that cystatin C improved risk prediction. The barrier to using cystatin C is that it is more costly, slower, and less available test than creatinine [40].

To overcome the problem of accurate assessment of the presence of CKD with age when should have evidence of structural damage or albuminuria or active urinary sediment or tubular damage nephrologists commonly find the e-GFR to be slightly below 60 mL/min/1.73 m^2 in elderly persons with no evidence of kidney disease who have a serum creatinine that is stable at a slightly elevated level [41].

The recent KIDGO classification of CKD was done to improve the clinical utility of the CKD stages; stage 3 was subdivided into stage 3a (45–59 ml/min/1.73 m^2) and stage 3b (30–44 ml/min/1.73 m^2), and urine albumin or protein was added in the classifications. Thus, if a patient were in stage 3a based on their GFR, but had normal excretion of protein in their urine and no other indications of kidney disease, this was useful to not to add burden for unnecessary follow-up of elderly patients, and there was no need for aggressive therapy for CKD patients who not fulfilling the complete diagnostic definition of CKD. Peralta et al. recommended using combined measurement of (e-GFR creatinine, e-GFR cystatin C, and urine albumin creatinine ratio) for early detection of diabetic kidney disease and predict mortality and development of end-stage renal disease [41].

This study had some limitations. This was a single-center and cross-sectional study and with a small number of recruited patients, and we did not assess the associated cardiovascular morbidities.

Conclusion

The use of estimated glomerular filtration rate by serum cystatin C is an early and better indicator of diabetic kidney disease than the estimation of glomerular filtration rate by serum creatinine as it had a higher sensitivity and specificity.

Abbreviations

DM	Diabetes mellitus
T1DM	Type 1 diabetes mellitus
AER	Albumin excretion ratio
Cys-c	Cystatin C
e-GFR	Estimated glomerular filtration rate
BMI	Body mass index
T2DM	Type 2 diabetes mellitus
(NICE)	National Institute for Health and Care Excellence
M-GFR	Measured glomerular filtration rate
CKD	Chronic kidney disease
UACR	Urinary albumin excretion ratio
ADA	American Diabetes Association
e-GFR creat	Estimated glomerular filtration rate by creatinine
e-GFR cys	Estimated glomerular filtration rate by cystatin C
CKD-EPI	CKD Epidemiology Collaboration

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Authors' contributions

AEz contributed to the data collection and writing of the introduction, results, discussion, and references. AEl contributed to the data collection and writing of the introduction and references. ROA contributed to the data collection and writing of the introduction, discussion, and results. WIG contributed to the data collection and writing of the introduction, results, discussion, and references.

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Availability of data and materials

The data supporting our findings are available if requested.

Declarations

Ethics approval and consent to participate

This study was approved by the ethical committee in the Benha Faculty of Medicine
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Consent for publication

A written and informed consent was taken from the participants before being involved in the study.

Competing interests

The authors declare that they have no competing interests.

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