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Review Article

Cystatin C and Its Role in Patients with Type 1 and Type 2 Diabetes Mellitus

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Diabetes mellitus is the commonest cause of CKD. It is the leading cause of new patients requiring renal replacement therapy, accounting for 40%, 34%, and 30% of cases in United States, Germany, and Australia, respectively. Recent studies have shown that a low-molecular weight protein, cystatin C, freely filtered by the kidneys is a novel biomarker that may be used for detection of early renal dysfunction in patients with type 1 or type 2 diabetes. Cystatin C has also been shown to detect cardiovascular disease in patients with diabetes and it may also be linked with incident type 2 diabetes in obese patients. We aim to review current evidence based literature on use of cystatin C for early detection of diabetic nephropathy due to type 1 and type 2 diabetes in comparison to conventional methods and explore its association with other comorbidities.

1. Introduction

Diabetic nephropathy is classically defined by the presence of proteinuria, in the absence of other renal disease. It is a common problem that is most likely to occur in patients who have poor glycemic control, hypertension, glomerular hyperfiltration, or a genetic predisposition. The lifetime risk of nephropathy is estimated to be equivalent in type 1 and type 2 diabetes [1]. It is more prevalent among African Americans, Asians, and Native Americans than Caucasians [2, 3].

Microalbuminuria precedes the development of macroalbuminuria and is predictive of future nephropathy. The onset of macroalbuminuria in the absence of effective therapy is followed by a slowly progressive decline in glomerular filtration rate (GFR) [4].

Current KDIGO guideline is the first to incorporate cystatin C based formulas in addition to creatinine and GFR estimating formulae when the latter are less accurate as in severe muscle wasting when tubular secretion of creatinine is affected by drugs. Moreover these can be used in special circumstances when knowledge of the exact GFR is important as in adjusting dosage of toxic drugs that are excreted by the kidneys or determining eligibility for kidney donation [5].

Screening for Microalbuminuria. In patients with type 2 diabetes screening for diabetic nephropathy must be initiated at the time of diagnosis, since >7% of them already have microalbuminuria at initial presentation [6, 7]. For patients with type 1 diabetes, the first screening has been recommended at 5 years after diagnosis [6]. However, in EURODIAB IDDM complication study group it is demonstrated that in type 1 diabetes the prevalence of microalbuminuria can reach 18% before 5 years, especially in patients with poor glycemic and lipid control and normal to high blood pressure levels [8]. Therefore, in type 1 diabetes, screening for microalbuminuria may be performed 1 year after diagnosis, especially in patients with poor metabolic control. If microalbuminuria

is absent, the screening must be repeated annually for both type 1 and 2 diabetic patients [6].

Monitoring of Renal Function. Although the measurement of UAE (urinary albumin excretion) is the cornerstone for the diagnosis of diabetic nephropathy, there are some patients with either type 1 or type 2 diabetes who have decreased glomerular filtration rate (GFR) in the presence of normal UAE [9, 10]. In patients with type 1 diabetes, this phenomenon is more common among females with longstanding diabetes, hypertension, and/or retinopathy [9]. For patients with type 2 diabetes in NHANES III (Third National Health and Nutrition Examination Survey), low GFR (<60 mL/min) was present in 30% of patients in the absence of micro- or macroalbuminuria and retinopathy [11]. Although renal biopsy was not performed, this observation was probably related to renal parenchymal disease rather than classical diabetic glomerulosclerosis. These studies indicate that normoalbuminuria does not predict decline in GFR in type 1 and type 2 diabetic patients.

GFR is the best parameter of overall kidney function [12] and should be measured or estimated in all diabetic patients for timely intervention in this population since large, prospective, randomized studies (UKPDS, STENO 2, and ADVANCE) have shown that early therapeutic intervention in diabetic patients can delay onset and progression of complications.

2. Methods of Estimating (GFR)

2.1. Clearance Methods. Measurements of GFR are traditionally based on the renal clearance of a marker in plasma, expressed as the volume of plasma completely cleared of the marker per unit time. The ideal marker should be endogenous, freely filtered by glomerulus, neither reabsorbed nor secreted by the renal tubule, and eliminated only by the kidney. Various markers used to measure GFR include exogenous (inulin and iothalamate) or endogenous (urea and creatinine) substances [13] (Table 1).

2.2. Prediction of GFR from Plasma Creatinine. In 1976, Cockcroft and Gault published an equation to predict creatinine clearance based on age, weight, height, and plasma creatinine, together with correction factors [14]. Although helpful, it has many inherent limitations.

Among adults, the MDRD study equation provides a clinically useful estimate of GFR (up to approximately 90 mL/min/1.73 m^2) (S). The MDRD study equation has the advantages of having been based on

(i) GFR measured directly by urinary clearance of 125-Iothalamate;

(ii) a large sample of >500 individuals with a wide range of kidney diseases;

(iii) inclusion of both European-American and African-American participants;

(iv) validation in a large ($n > 500$) separate group of individuals as part of its development [15].

In May 2009, Levey et al. reported that the CKD-EPI creatinine equation was somewhat more precise than the MDRD study equation, especially at higher GFRs. Using the new equation could decrease false-positive results [16].

3. Cystatin C as a Method of Estimating GFR

Cystatin C is considered a good marker of kidney function as it is filtered solely by the glomerulus, is not handled by the renal tubules, and is generated at a constant rate by all cells in the body.

Two meta-analyses have concluded that serum cystatin C is superior to serum creatinine as a marker of kidney function [17, 18]. One of them evaluated Twenty-nine studies (21 in adults) reported before 2009 which, compared serum creatinine with cystatin C in CKD patients. Of those, 17 showed that cystatin C was a better predictor of GFR, while 12 showed no difference in the prediction of GFR [18]. When compared to MDRD formula, the cystatin C formula is more likely to be predicted if GFR is below or above 60 mL/min/1.73 m^2 ($P < 0.0005$) [19]. The addition of age, sex, and race to cystatin C helps make it more accurate, but combining these factors with serum creatinine may provide the best estimation of GFR. In a recent study by Levey et al., an equation that used both serum creatinine and cystatin C with age, sex, and race was better than equations that use only one of these markers [16]. Other authors suggested that an equation that uses both serum creatinine and cystatin C with age, sex, and race would be better than equations that use only one of these serum markers [20, 21].

3.1. Clinical Considerations with Varying Degrees of Kidney Function

3.1.1. Early Kidney Disease. Cystatin C may detect mild-to-moderate decreases in GFR that are not evident with serum creatinine-based measurements. Some studies suggest that CysC-GFR was better than creatinine-based estimates of GFR at GFR levels >60 mL/min/1.73 m^2 (CKD stages 1 and 2) [22].

In addition, Cys-GFR appeared to be better correlated with microalbuminuria, while MDRD and CG creatinine estimates of GFR tend to reflect only proteinuria [21]. Using CysC-GFR, over one-third of type 1 diabetes patients with microalbuminuria at the time of enrollment already had evidence of mild (CysC-GFR < 90) or moderate (CysC-GFR < 60 mL/min/1.73 m^2) CKD [23].

3.1.2. Kidney Transplantation. CysC-GFR after transplant has been used to detect allograft dysfunction and monitor drug nephrotoxicity, with reported diagnostic value [24]. In kidney transplant patients, cystatin C was reported to be more sensitive than serum creatinine for detecting decreases in GFR and delayed graft function, offering an opportunity for timely intervention [25].

Follow-up studies have found that GFR was overestimated by 30% when derived from plasma creatinine levels [26]. On the other hand cystatin C underestimated GFR

Table 1

Exogenous substances	Characteristics and advantage	Disadvantages
Inulin (MW 5200 Dalton)	(i) Considered the gold standard for the estimation of GFR. (ii) It is freely filtered by glomerulus and is neither reabsorbed nor secreted by the renal tubules. (iii) Metabolically inert and cleared only by the kidney. (iv) It requires constant IV infusion to maintain plasma level and once steady state has been achieved, plasma and timed urine specimen levels are measured.	Analysis of inulin is technically demanding, time-consuming, labor intensive, costly, and unsuitable for outpatient use.
Nonradiolabelled contrast media **(iothalamate/iohexol)**	It has the advantage that urography and an estimation of GFR can be done at a single examination.	Cannot be used for routine to assessment of GFR.
Radiolabelled compounds	Radiolabelled compounds include [51Cr] EDTA, [125I] iothalamate, [99Tcm] DTPA, and [131I] Hippuran.	Cannot be used for routine to assessment of GFR.
Endogenous substances		
Urea (MW 60 dalton)	One of the first markers for assessing GFR	Urea production is variable and is influenced by many substances.
Creatinine (MW 113 daltons)	First introduced by Popper and Mandal [27]	(i) Dependent on muscle mass, which varies with age, gender, and weight. (ii) Some secretion by the renal tubules. (iii) Difficulty of obtaining complete, accurately timed urine collections. (iv) High protein intake leads to 10% increase in plasma creatinine. (v) Drugs like triamterene, spironolactone, amiloride, probenecid, cimetidine, trimethoprim, high dose salicylates, or pyrimethamine inhibit tubular secretion and induce true elevation of plasma creatinine.

by 14%, and it was still more sensitive in detecting kidney damage, with no false-negative results [28].

3.1.3. Acute Kidney Injury (AKI). Serum cystatin C has been reported to outperform conventional biomarkers in the prediction of AKI and to have prognostic value of the need for kidney transplant and in-hospital mortality [29]. Cystatin C has been reported to increase about one to two days earlier than serum creatinine in patients developing AKI. AKI is not rare in hospitalized patients, with a mortality rate estimated to be between 30% and 90% [30].

4. Cystatin C in Type 1 Diabetes

In the early 1980s, three landmark studies of patients with type 1 diabetes identified "microalbuminuria" as the first detectable functional abnormality [31–33]; however, estimation of GFR remains critical to assessment of renal function.

Tan et al. carried out the first published study, which simultaneously examined the relative precision and correlation of plasma cystatin C with routine clinical measures and a reference method (GFR-IO). This study included 40 volunteers with normal plasma creatinine levels. Twenty-nine subjects were type 1 diabetic patients with varying degrees of albuminuria. The authors demonstrated that cystatin C proved to be more reliable than 24-hour creatinine clearance and was superior to plasma creatinine as well as the Cockcroft-Gault estimation. Amongst a subgroup of 8 diabetic patients (with GFR-IO less than the minimum value in nondiabetic subject), only 2 were identified with subnormal GFR using plasma creatinine whereas all 8 subjects were shown to have elevated serum cystatin C concentrations. Additionally, 14 diabetic subjects were noted to have increased serum cystatin C concentrations compared to only 1 patient with elevated plasma creatinine levels when analyzed against the gold standard reference measures [34]. Observations from this study led to the conclusion that, in patients with type 1 diabetes, cystatin C is a promising new marker of early renal dysfunction as it is more accurate than current measures for GFR estimation.

Subsequently, Buysschaert et al. assessed the performance of cystatin C in 46 patients with type 1 diabetes spanning a wide range of renal functions in comparison to serum creatinine. This study also concluded that serum cystatin C is a better determinant of estimated GFR when compared to the conventional serum creatinine measurement [35]. Both these

studies demonstrated that serum cystatin C performed better than serum creatinine in the evaluation of renal dysfunction in patients with type 1 diabetes.

Christensson et al. investigated the accuracy of serum cystatin C versus serum creatinine for the early detection diabetic nephropathy in addition to the effect of age on these two GFR markers. This study included a large cohort of type 1 ($n = 41$) and type 2 ($n = 82$) diabetic patients. Serum cystatin C was shown to have no major advantage versus age-adjusted serum creatinine in the evaluation of GFR < 60 mL/min. However, it is important to note that serum cystatin C was more effective in the diagnosis of mild diabetic nephropathy (as defined by GFR < 80 mL/min) than serum creatinine suggesting that serum cystatin C is useful for the identification of early diabetic nephropathy [36].

In a more recent study, Pucci et al. compared the accuracy of cystatin C with creatinine and the Cockcroft-Gault formula and MDRD study equation for the assessment of early decline in renal function in diabetic patients with renal impairment. It included the largest cohort of type 1 diabetic patients ($n = 125$) and demonstrated that cystatin C better correlated with GFR than creatinine-based formulae. This study also proved that cystatin C is more sensitive for detecting early renal function impairment than creatinine and creatinine-based formulae. The mean cystatin C concentrations showed statistically significant stepwise increase as GFR declined allowing very early detection of reduction in renal function. Interestingly, at GFR cut-points of 90 mL/min and 75 mL/min, the diagnostic efficiency of cystatin C was better [37].

Furthermore, over a median 23 years of follow-up, cross-sectional and longitudinal analyses of 1441 participants in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study with type 1 diabetes revealed that mean rate of change in eGFR was similar when estimates were calculated using creatinine, cystatin C, or both markers. The association of BP and HbA_{1c} with change in eGFR was strongest for estimates calculated using cystatin C and, a combination of creatinine and cystatin C. This study demonstrated that use of cystatin C in addition to creatinine might not be of significance in clinical practice; however, it has the potential to further unravel the pathophysiological changes leading to loss of GFR in type 1 diabetes [38].

5. Cystatin C in Type 2 Diabetes Mellitus

Screening for diabetic nephropathy is recommended as early intervention delays the progression of kidney disease [39]. So far annual screening for microalbuminuria is the modality used for detecting diabetic nephropathy [40]. Recently, interest has grown in the use of another surrogate marker, cystatin C, in detection of renal disease in type 2 diabetes mellitus. It has been noted that patients with type 2 diabetes and microangiopathy have statistically significant higher levels of cystatin C than healthy individuals [41]. In 52 Caucasian patients with type 2 diabetes, cystatin C was found to be a better marker of kidney disease measured by serum creatinine or Cockcroft and Gault GFR estimation. The study clearly demonstrated that serum concentration progressively increased as glomerular filtration rate decreased [42].

Similarly, Mojiminiyi et al. conducted studies in Kuwait to evaluate the role of cystatin C in patients with type 2 diabetes mellitus. In one study, they evaluated the use of cystatin C as a marker of nephropathy in 77 patients with type 2 diabetes who were normoalbuminuric, microalbuminuria, and macroalbuminuric. In this study with microalbuminuria being the "gold standard," the sensitivity of cystatin C was 40% and the specificity was 100% for the detection of nephropathy. Cystatin C identified 40% of the patients with diabetic nephropathy as compared to serum creatinine, which only identified 12% [43]. In another study, cystatin C, beta-2 microglobulin, and serum creatinine were measured in 105 patients with type 2 diabetes mellitus and compared to the measured creatinine clearance and the estimated creatinine clearance using the Cockroft and Gault formula. Cystatin C was found to have the highest sensitivity for detection of estimated creatinine clearance of less than 60 mL/min/1.73 m^2 at routine cut-off values. Additionally, cystatin C was best for discriminating between microalbuminuria and normoalbuminuria in those with type 2 diabetes resulting in the conclusion that cystatin C might be a more useful marker than creatinine for detection of early diabetic nephropathy in type 2 patients with diabetes [44].

In Egypt, El-Shafey et al. have demonstrated the usefulness of cystatin C in a small study that included 40 patients with type 2 diabetes mellitus. Cystatin C showed significant correlation with serum creatinine, creatinine clearance, and 24-hour urinary albumin [45]. Another small study demonstrated the superiority of cystatin C in detecting early disease in type 2 diabetes patients as compared to routine tests. Cystatin C detected renal abnormality in 19% of patients not diagnosed by routine tests. Hence, the authors recommended incorporating cystatin C when testing for renal function [46]. Similar results have also been reported by other study groups who propose the use of cystatin C based formulae as it has been shown to be comparable [47] or superior [48] to creatinine-based estimations of GFR in patients with type 2 diabetes.

In a recent study, Jeon et al. examined the relationship between cystatin C and albumin to creatinine ratio (ACR). Increase in levels of serum cystatin C was noted with progression of CKD from stages I to III. Also, rise in serum cystatin paralleled progression from normoalbuminuria to microalbuminuria, thereby revealing a positive correlation between serum cystatin C and ACR. The investigators concluded that serum cystatin C is a useful in early detection of diabetic nephropathy as it reflects reduction in GFR as well as rise in ACR [49]. The role of serum and urinary cystatin C in impaired renal function in addition to the optimum cut-off point at which impaired renal function may be detected has been evaluated in 742 patients with type 2 diabetes. Therefore, the investigators concluded that urinary cystatin C and duration of diabetes could be used as indicators of early renal damage [50].

6. Cystatin C as a Predictor of CV Disease in Diabetes Mellitus

Like microalbumin, cystatin C is linked to cardiovascular disease. It was shown that cystatin C level, independent of renal function, was associated with insulin resistance and inflammation. This may explain the association between cystatin C and cardiovascular disease in type 2 diabetes [51].

Furthermore, there is mounting evidence that cystatin C may be a predictor of adverse outcomes independent of renal function. Higher levels of cystatin C have been associated with a twofold increased risk of cardiovascular events even after adjusting for well-known risk factors [52] in addition to higher mortality in patients with acute coronary syndromes [53]. In unadjusted models, higher concentrations have been associated with the degree of endotheliosis in conditions believed to be attributable to endothelial damage [54].

In a recent trial Panaich et al. have tried to explore the link between cystatin C and anthropometric measures and its influence on cardiovascular mortality, and they found that cystatin C corelated better with measures of visceral adiposity that included waist circumference and waist to hip ratio compared to BMI. It appeared to predict cardiovascular outcomes better in those with measures that do not suggest obesity than those who have abnormal anthropometric measures [55].

Maahs et al. examined the hypothesis that, in patients with Type 1 diabetes, cystatin C could predict progression of subclinical coronary atherosclerosis (SCA). Additionally they postulated that this biomarker would be a stronger predictor of SCA compared to serum creatinine and commonly used creatinine-based formulae. This is the first study to compare cystatin C to other measures of renal function as a predictor of SCA in this particular subpopulation. The investigators concluded that increasing serum cystatin C was a better predictor of SCA progression than serum creatinine and serum creatinine derived estimates of GFR [56]. This observation is consistent with findings from previous studies in other populations; however, more evidence is required to validate these findings and provide insight into the association between cystatin C and coronary artery disease.

Trying to explore the link between cystatin C and increased cardiovascular risk, Lee et al. studied 478 patients with type 2 diabetes mellitus. They measured the degree of insulin resistance by using the homeostasis model assessment (HOMA-IR) and indicators of metabolic syndrome. Estimated glomerular filtration rate (eGFR) was derived from the MDRD equation. After adjusting for age, sex, body mass index, and eGFR, the cystatin C level increased significantly in proportion to the number of metabolic syndrome components present. The authors concluded that cystatin C is significantly associated with insulin resistance and biomarkers reflecting inflammation independent of renal function. These components may have a role in addition to that of eGFR in explaining the link between cystatin C and CVD in type 2 diabetes mellitus patients [51].

7. Cystatin C as a Predictor of Diabetes Mellitus

There is growing interest in the association of cystatin C and the development of type 2 diabetes mellitus. A cohort of 3472 nondiabetic individuals was followed up for 15 years where the incidence of diabetes was found to be 9.6% (diabetes defined as treatment with insulin, oral hypoglycemic agents, and/or diet or high levels of HbA_{1c}). The incidence was highest in those with higher cystatin C levels at baseline independent of confounding risk factors. Future research should be directed to evaluate the possible role of cystatin C in the pathogenesis of type 2 diabetes [57]. Reutens et al., in their study to evaluate the association between cystatin C and incident diabetes mellitus, included 2849 patients without overt nephropathy and found that cystatin C levels at baseline, after adjustment for age and gender, were significantly associated with incident diabetes on univariate analysis ($P = 0.0001$). This association was independent of baseline kidney function, fasting blood glucose, and HbA_{1c} levels. When BMI, waist circumference, and baseline insulin resistance were used as covariates they showed an interaction with cystatin C levels. They concluded that cystatin C was associated with incident diabetes but only in those with central adiposity or insulin resistance [58].

8. Contraindications to Use of Cystatin C

Cystatin C levels change with alterations in thyroid function and should not be considered for evaluation of GFR without assessing thyroid function tests [59]. They are also liable to change in patients with CKD receiving glucocorticoids [60].

9. Conclusion

Cystatin C is an important marker in detecting early kidney dysfunction in both type 1 and type 2 diabetes compared to creatinine based formulae. It is also an important predictor of cardiovascular disease in patients with diabetes. Recent studies have stated the association between cystatin C and incident type 2 diabetes, especially in obese patients.

Cystatin C has a potential to be used in in early detection of diabetic nephropathy, even before development of microalbuminuria, which will allow for timely intervention and management of diabetic nephropathy. However, it is currently not widely available and not all assays have been universally calibrated. Both these factors limit its use in clinical practice at present.

We suggest that future studies utilize cystatin C to study the changes occurring in diabetic nephropathy due to glomerular damage and tubular damage in addition to further assessing its relationship with decline in renal function due to type 1 and type 2 diabetes.

Abbreviations

CKD: Chronic kidney disease
GFR: Glomerular filtration rate
UAE: Urinary albumin excretion

NHANES: Third National Health and Nutrition Examination Survey
UKPDS: United Kingdom prospective diabetes study
AKI: Acute kidney injury
HOMA-IR: Homeostasis model assessment of insulin resistance.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Alaaeldin M. Bashier wrote (cystatin C and incident diabetes, cystatin C and CVD, abstract, and conclusion), reviewed, and edited the paper. Ayman Aly Seddik Fadlallah wrote (Methods of GFR detection), edited, and reviewed the paper. Nada Alhashemi wrote the paper (cystatin C in type 2 diabetes). Puja Murli Thadani wrote the paper (cystatin C in Type 1 Diabetes). Elamin Abdelgadir reviewed the paper and edited it. Fauzia Rashid wrote the paper (Introduction).

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