The Usefulness of Cystatin C as a Marker for Chronic Kidney Disease

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Abstract

Background: Diagnostic marker to detect chronic kidney disease (CKD) at early stage is important as early intervention can slow the loss of kidney function. Plasma or serum Cystatin C (CysC) is said to be a superior marker for CKD compared to serum creatinine (SCr) to detect mild GFR reduction between 60 and 90 mL/min/1.73m². Methods: We analysed blood and urine samples from 418 normal subjects and 37 Type 2 diabetes patients (T2DM) with CKD. Estimation of glomerular filtration rate (eGFR) was determined using CKD-EPI. We compared the level CysC by CKD staging. Then, the correlation CysC and eGFR were compared between the normal subjects and the T2DM patients. Results: Plasma CysC level increase with the progression of CKD and was significantly elevated in CKD stage 2. CysC levels were highly correlated with eGFR in the T2DM patients. Conclusion: These results indicated that CysC have the potential of detecting early CKD especially in those with high risk such as the T2DM patients and also hypertension.

Keywords

Chronic Kidney Disease; Cystatin C; Estimated Glomerular Filtration Rate; Albumin - Creatinine Ratio; Diabetes; Hypertension

1. Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) in particular are major health problems worldwide with dramatically rising incidence and prevalence. Substudy of the National Health and Morbidity Survey 2011 showed that the prevalence of chronic kidney disease of the adult population (over 18 years old) in West Malaysia was 9.07% [1]. It is also a growing problem in other Asian countries, partly due to the rising prevalence of non-communicable diseases such as diabetes and hypertension [2].

CKD patients are often asymptomatic, and thus, a laboratory measurement of kidney function is required. In practice, serum and plasma creatinine are the most widely used endogenous markers of glomerular filtration (GFR). The sensitivity of serum creatinine in the detection of CKD is poor and it will fail to identify half of the patients with crucial stage 3 CKD (GFR of 30-59 mL/min/1.73m²) [3],[4],[5] as serum creatinine concentration may not change until approximately 50% of the kidney function has been lost [6]. Furthermore, creatinine production is also influenced by factors such as age, gender, muscle mass, physical activity and diet [7]. Due to the many problems encountered with measurements of creatinine and its use as a GFR estimate, cystatin C (CysC) has been proposed as an alternative marker of renal function.

Cystatin C is a 13-kDa, non-glycosylated basic protein belonging to the cystatin super-family of cysteine proteinase inhibitors. Studies have shown that CysC may be more sensitive in identifying mild reductions in kidney function than serum creatinine (SCr) [8],[9]. It is produced at a stable rate, which is unaffected by inflammatory processes, sex, age, diet, and nutritional status [10]. However, owing to its relatively recent introduction, there are only limited numbers of studies for CysC in the Asian general population. The aim of this study was to examine the usefulness of CysC as a marker for CKD.

2. Materials and Methods

This was a cross-sectional study involving sub-sample of the National Health and Morbidity Survey 2011 who consented to participate in the CKD study and Type 2 diabetes with CKD patients (T2DM) from the General Hospital Kuala Lumpur. For the NHMS, a stratified two-stage cluster sampling design was used to draw a sample of 9258 private dwellings [11]. For the CKD substudy, only respondents from West Malaysia were selected [12]. Subjects who agreed to participate were requested to fast for 10-12 hours prior to the study visit. Exclusion criteria were pregnant women or those menstruating during data collection. This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia.

Blood sampling for serum creatinine and early-morning urine sampling for urine ACR estimation were obtained by hemodialysis personnel from the nearest Ministry of Health
hemodialysis unit. Blood and urine samples were sent by express courier to Institute for Medical Research Kuala Lumpur (central laboratory) for analysis and storage. Blood samples were processed for plasma, and creatinine, CysC and other chemistry laboratory tests which coincided with creatinine clearance measurement were analyzed on Selectra XL Chemistry Analyzer (Vital Scientific, Dieren, The Netherlands) using reagents purchased from Randox Laboratories (Antrim, UK). The Jaffe method was used to measure creatinine, and has calibration traceable to an isotope dilution mass spectroscopy reference method. Interassay coefficient of variability (CV) for creatinine at 124 and 303 mmol/l was 6.2% and 4.7%, respectively, and for microalbumin at 32.2 and 159mg/l was 8.0% and 3.6%, respectively. Latex Enhanced Immunoturbidimetric method was used to measure CysC. Inter-assay CV for CysC at 0.78 mg/l and 3.37 mg/l was 3.1% and 1.3% respectively. A1C was determined by automatic reversed-phase cation exchange based chromatography method (Adams HA-8160). eGFR was derived for these subjects using the CKD-EPI equation as follows:

\[
141 \times \min \left( \frac{SCr}{k}, 1 \right)^{\alpha} \times \max \left( \frac{SCr}{k}, 1 \right)^{-1.209} \times 0.993^{\text{Age}} \times \left( 1.1018 \text{ if female} \right)
\]

Where SCr is serum creatinine (in mg/dl), k is 0.7 for women and 0.9 for men, \( \alpha \) is -0.329 for women and -0.411 for men, min is the minimum of SCr/k or 1, and max is the maximum of SCr/k or 1.

2.1. Definitions

Microalbuminuria was defined as urine ACR 30–300mg/g. Macroalbuminuria was defined as urine ACR of ≥ 300mg/g [12]. CKD stages 1 and 2 were defined as eGFR ≥90ml/min per 1.73m² and 60–89ml/min per 1.73m², respectively, urine ACR ≥30mg/g. Stages 3, 4, and 5 were defined as eGFR 30–59, 15–29, and ≤ 15ml/min per 1.73m², respectively, regardless of kidney damage [13],[14]. Hypertension was defined as the average of two BP readings with systolic BP ≥ 140 and/or diastolic BP ≥90mmHg [15] and/or self reported hypertension previously diagnosed by medical personnel.

2.2. Statistical Method

Data analysis was done by exporting the raw data into SPSS (version 16, Chicago, IL). Data are presented as mean ± SD. The differences of the data among CKD stages were investigated by One Way ANOVA test. P < 0.01 was considered statistically significant. Correlations between CysC and eGFR were investigated using non-linear regression analysis and by calculating the coefficient of regression (R).

| Table 1. | Baseline Characteristics of NHMS-CKD subjects and T2DM patients with CKD. Data are expressed as mean ± SD. |
| --- | --- |
| NHMS-CKD Substudy | T2DM with CKD |
| n | 418 | 37 |
| Gender | | |
| Male | 210 | 18 |
| Female | 218 | 19 |
| Sociodemographic characteristics | | |
| Age | 43±15 | 54±11 |
| Current Smokers (n) | 91 | - |
| Hypertension (n) | 156 | 30 |
| BMI (kg/m²) | 25±5.6 | 27±4.3 |
| Waist Circumference (cm) | 87.4±14 | 102.2±12.6 |
| HbA1c (mmol/mol) | 40±15.5 | 70±16.5 |
| Serum Creatinine (mg/dl) | 0.7±0.2 | 1.5±0.8 |
| Cystatin C (mg/l) | 0.8±0.2 | 1.3±0.8 |

| Table 2. | Proportion of subjects with CKD |
| --- | --- |
| NHMS-CKD Substudy % (n) | T2DM with CKD % (n) |
| Normal | 78.9 (330) | - |
| Stage 1 | 14.4 (60) | 8.1 (3) |
| Stage 2 | 5.5 (23) | 27.0 (10) |
| Stage 3 | 1.2 (5) | 43.2 (16) |
| Stage 4 | - | 21.6 (8) |
3. Results

A total of 418 subjects from the NHMS-CKD and 37 T2DM patients with CKD participated in the study. The profiles of the subjects with mean age of 43.1±14.9 and 53.7±11.0 respectively are shown in Table 1. Of the NHMS-CKD subjects 78.9\% was normal, 14.4\% have CKD stage 1, 5.5\% CKD stage 2 and 1.2\% CKD stage 3 (Table 2). Subjects with CKD had higher SCr, CysC and HbA1c value, 0.77±0.1mg/dl, 0.88±0.28 mg/L and 50.18 ± 23.32 respectively (Table 3).

By ACR, 78.2\% subjects have normoalbuminuria, 14.8\% have microalbuminuria and 6.9\% have macroalbuminuria (Table 4). Plasma CysC levels increased with the progression of CKD staging. Comparison of CysC value in the three subgroups (CKD stage 1, 2 and 3) of CKD showed that CKD stage 2 and 3 subjects have higher CysC concentrations compared to the normal subjects and also showed statistically significant differences between the subgroups (Fig.1).

Of the T2DM patients, 8.1 \% have CKD stage 1, 27 \% have CKD stage 2, 43.2\% have CKD stage 3 and 21.6\% have CKD stage 4. By ACR, 47.4\% of the T2DM patients have microalbuminuria and 42.1\% macroalbuminuria while the rest were normoalbuminuria. The T2DM patients have significantly higher CysC value (1.3 ± 0.77 mg/l) in comparison to the NHMS-CKD subjects. Similar to the NHMS-CKD subjects, the T2DM patients CysC level showed statistically significant differences between the subgroups (Table 2) except for CKD stage 1.

![Figure 1. Plasma CysC levels in each stage of chronic kidney disease. The subjects classified to CKD staging as follow: CKD stages 1 and 2 were defined as eGFR ≥90 ml/min per 1.73 m² and 60–89 ml/min per 1.73 m², respectively, with urine ACR ≥ 30 mg/g. Stages 3, 4, and 5 were defined as eGFR=30–59, 15–29, and ≤ 15 ml/min per 1.73 m², respectively, regardless of kidney damage. Serum CysC increased with the progression CKD, and it was significantly higher in the subjects with mild to moderate eGFR (stages 2 and 3), but not significant in stage 1. Error bars indicate S.D. for statistical significance (One Way ANOVA test). * p<0.01]
The correlations of CysC to eGFR were compared between the NHMS-CKD subjects with CKD and the T2DM patients with CKD (Fig. 2). Both correlated significantly with eGFR but CysC was highly correlated with eGFR in the T2DM patients with CKD ($R^2 = 0.85$).

Out of 407 NHMS-CKD subjects, 33% (91) were hypertension (Table 1) and have significantly elevated CysC of $0.9 \pm 0.2$ mg/L as compared to those without hypertension (Fig.3). Similarly, the level of CysC was significantly elevated among smokers (Fig. 3).

### 4. Discussion

It is important to have reliable marker to detect early stage of CKD, that is stage 1 and stage 2 so that early treatment can be instituted. Late detection or untreated CKD can result in end-stage renal disease and necessitate dialysis or kidney transplantation. In this study we found that plasma CysC level become significantly elevated at CKD stage 2 among normal adults. The mean value of subjects with CKD stage 2 in the study has exceeded the upper limit of normal recommended for this technique [15]. The range of CysC of our normal subjects with CKD stage 2 and 3 was $0.7-1.7$ mg/l and was within the cut off value suggested to detect CKD stage 2 and 3 [17],[18]. These support the potential utility of CysC to detect early renal failure i.e at CKD stage 2 [19]. It was also shown that elderly subjects with elevated CysC ($\geq 1.0$ mg/l) had a fourfold risk of progressing to CKD after four years of follow up compared to those with normal CysC concentrations suggesting the potential of CysC to identify a “pre-clinical” state of kidney dysfunction [20].

The relationship between CysC and GFR differed across clinical presentations. Cystatin C has been demonstrated to be more accurate than serum creatinine in the detection of early renal impairment and in specific populations may allow for early detection of renal disease. Rule et al., [21] showed that the association between CysC and GFR was stronger among native kidney disease patients than in healthy persons. In this study, we found that CysC correlation with eGFR differ significantly between the normal subjects and the T2DM patients. T2DM showed better correlation with the eGFR compared to the normal subjects. This suggests the advantage of using CysC for CKD detection in T2DM patient over general population. Evidence is mounting that CKD screening should be implemented in certain high risk groups (e.g., older patients, patients with hypertension) in addition to patients with diabetes [22][23][24]. Similarly, National Kidney Foundation of USA and the not-for-profit organization KDIGO (Kidney Disease – Improving Global Outcomes) recommending ‘All countries should have a targeted screening programme for CKD’ – focusing on those people known to have diabetes, hypertension and cardiovascular disease[25][26]. Given the ease of identification of the high-risk groups, CysC may be useful to establish the presence of and the staging of CKD.

Mild to moderate reductions in kidney function are relatively common in hypertensive patients, and are also associated with increased risk for cardiovascular events[27]. The association of CysC and cardiovascular risk has been previously studied [28][29]. Elevated CysC was shown to be associated with classical cardiovascular risk factors such as diabetes, hypertension and chronic renal disease [28]. In our study, subject with hypertension showed significantly higher CysC level compared to those without hypertension. Also, in our general population CysC was significantly elevated among smokers than non-smokers. These results suggested that CysC would be not only practical in early recognition of CKD but may also relate to classical cardiovascular risk factor such as hypertension and smoking. Thus, confirmatory screening (e.g., a quantitative
measurement such as urine albumin-to-creatinine ratio) and follow-up in those with risk will improve the clinical outcome. In addition, CysC may provide new insights into the importance of the relationship between kidney disease and hypertension in subjects with presumably normal renal function. [27]

This study was performed in a normal subjects and T2DM patients with CKD. T2DM is well recognized as a risk factor for CKD [30]. Our result showed that CysC is a useful marker to recognise stage 2 CKD and it correlated well with eGFR in T2DM patients suggesting that CysC would work better in providing early recognition of CKD in individuals at high risk for CKD. This highlights the potential usefulness of screening for moderate or mild CKD in subjects with diabetes by measuring CysC levels. Although Knight et al.[9] found that serum cystatin C level alone was a better predictor of creatinine clearance than serum creatine level, however, when they incorporated clinical information such as age, weight, and gender into their models, serum cystatin C level did not perform better than serum creatine level for predicting creatinine clearance. Their data also showed that taking into account age, weight, and gender improved the predictive performance of serum cystatin C level, albeit to a smaller extent than serum creatine level. Thus, caution must be used when interpreting cystatin C levels alone. More studies are needed to determine the best equation to be used for the estimation of filtration rate by CysC.

Our limitation was not using iothalamate clearance as the gold standard of kidney function measurements of GFR as recommended [31][32], however early-morning spot urine ACR has also been shown to be sensitive and high specificity measure for detection of kidney damage [32].

5. Conclusion

Despite that both creatinine and CysC can be both easily and rapidly determined, CysC testing is more costly than creatinine but it has been shown to be a reliable marker in detecting early changes in GFR [33][34][35].

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