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Comparison of Estimated Glomerular Filtration Rate between Cystatin C and Creatinine in Children with Chronic Kidney Disease

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Abstract

Background: Glomerular Filtration Rate (GFR) becomes essential in Chronic Kidney Disease (CKD) to detect renal impairment as early as possible to improve the outcome. Cystatin C has been proposed recently as a better marker for estimated GFR (eGFR) beyond creatinine and its limitation.

Objective: To compare the creatinine and cystatin C as markers for estimation of GFR in children with chronic kidney disease.

Methods: This was a cross sectional study conducted among children with CKD that were admitted to tertiary hospital at H.Adam Malik Hospital Medan. We took the blood serum samples to measure creatinine and cystatin C levels and determined both eGFR by using CKD-EPI equations. Gender, age, body weight and body height were also evaluated to know its association with the eGFR. The performance of both markers of eGFR were then assesed by correlation and agreement methods using Mc Nemar and Blant Altman analysis.

Results: The total number of samples in this study were 36 participants with mean age of 10,1 years. There was significant difference between eGFR based on creatinine and cystatin C (mean difference 36.9, 95 % CI 29.0 to 44.9, P=0.001). Proportion between eGFR based on creatinine and cystatin C to determine normal and decreased renal function showed significant difference (P=0.001) in this study.

Conclusion: There is a significant difference between creatinine and cystatin C for estimation of GFR in early stage of CKD in children.

Keywords: Chronic kidney disease; Estimated GFR, Creatinine, Cystatin C

Introduction

Chronic Kidney Disease (CKD) in children has become public health problems with the increasing prevalence each year [1,2]. CKD is defined as either structural or functional abnormality of kidney which lasts for more than three months with impact on health, with or without the decrease in renal function and also can cause the incidence of kidney failure or even of death [3,4].

Glomerular Filtration Rate (GFR) is the best examination to determine renal function and is really important in CKD to be able to detect, evaluate, and manage CKD accurately [5-7]. we can perform the measurement of GFR by using exogenous and endogenous markers while the exogenous (also known as direct or measured GFR) is the most accurate one but is rarely done in daily examination since it is impractical, expensive and scanty materials, and complicated procedure, particularly in children [5-8].

Creatinine is one of the endogenous markers to measure the GFR which is the most commonly used and has become the standard in classifying GFR internationally [9,10]. The equation of GFR based on creatinine in children is influenced by age, gender, and body height so that it is assumed that it is impractical and inaccurate [11,12]. The value of creatinine has not also been able to detect the decrease in GFR when it is on the level of 60-90mL/min/1.73m2 or CKD in stage II which is known as 'the creatinine blind area' [13,14].

Cystatin C is an alternative marker which is considered better than creatinine in evaluating GFR [9,15,16]. A meta-analysis study in 2007 on the significant difference between cystatin C and creatinine as the indicator of renal function in children revealed that assaying GFR with cystatin C was better than that with creatinine serum [17]. Another research conducted in

Indonesia in 2014 on the difference in GFR based on creatinine and cystatin C serum in children's nephrotic syndrome indicated that there was significant difference between these two estimated GFR [18].

Methods

Study design and sample

Cross-sectional study was conducted in January 2016 - March 2016 at Haji Adam Malik Hospital Medan, Indonesia, among children who were 2-18 years old and suffered from CKD taken by using consecutive sampling technique. Patients who underwent renal replacement therapy or with malignancy were excluded in this study.

Measurement of GFR

We took blood serum samples of all subjects to measure the level of creatinine and cystatin C serum and to estimate the eGFR using the latest equations from the Chronic Kidney Disease Epidemiology (CKD EPI) Collaboration. Creatinine was determined enzymatic ally using the ARCHITECT cSystems. Cystatin C concentrations were determined by means of particle-enhanced immunonephelometry using BN System from Siemens. We also assessed the age, gender, body weight and body height to determine the association with the difference of estimated GFR based on cystatin C and creatinine. This study was approved by the Medical Ethics Committee of the Faculty of Medicine, University of Sumatera Utara.

Statistical analysis

The gathered data were processed and analyzed using computerization and SPSS software program. Chi square test and Fischer test were used to assess the comparison between creatinine and cystatin C in assessing CKD classification based on their stages. Mc Nemar test was used to find out the difference in proportion between the estimation of GFR based on creatinine and cystatin C in assessing the decrease in GFR<90mL/minute/1.73m2. Non-paired t-test and linear regression test were used to assess the correlation of the estimation of GFR based on cystatin C and creatinine with the factors which influenced it. Blant-Altman analysis was used to determine the agreement between cystatin C and creatinine in assessing the eGFR. Significance level was applied when $p<0.05$ and the significance level was 95%.

Results

There are 36 participants with mean age of 10.1 years and same proportion between the subjects who were less than 10 years old and more than 10 years old. There were 19 of the patients males and 17 of them were females, 18 patients were underweight and 2 patients had normal height (normoheight). Mostly of the patients (27) had the nephrotic (NS) as the etiology which caused the CKD while congenital abnormality of kidney and urinary tract (CAKUT) and other disease (SLE, complex urinary tract infection) contributed 3 and 6 samples respectively.

The result of laboratory assay showed that the mean of creatinine was 0.9mg/dl with standard deviation of 1.19 and the mean of cystatin C was 1.4mg/dl with standard deviation of 1.24. The mean of eGFR based on creatinine in patients was 109.7mL/min/1.73m2 with standard deviation of 51.56 while the mean of eGFR based on Cystatin C was 72.8mL/min/1.73m2 with standard deviation of 28.12. There was significant difference between the estimation of GFR based on creatinine and cystatin C (mean difference of 36.8, 95% CI 29.0-44.9, P=0.001) (Table 1).

Table 1: Baseline characteristics of participants.

Characteristics	(N =36)
Age (years), mean (SD)	10.1 (4.38)
Gender, n	
Male	19
Female	17
Body weight status, n	
Normoweight	15
Underweight	18
Overweight	3
Body height status, n	
Normoheight	20
Stunted	16
Etiology of CKD, n	
Congenital abnormality of kidney and urinary tract (CAKUT)	3
Nephrotic syndrome	27
Others (SLE,Complex UTI)	6
Creatinin, mean(SD), mg/dl	0.9(1.19)
Cystatin C, mean (SD), mg/L	1.4(1.24)
eGFR Creatinin (ml/min/1,73m2), mean (SD)	109.7(51.56)
eGFR Cystatin C(ml/min/1,73m2), mean (SD)	72.8(28.12)

Table 2: Correlation of sex, age, body weight, and body height with the estimation of GFR using creatinine and cystatin C.

Characteristics	N	eGFR Creatinin, mean (SD), mg/dl	P	eGFR Cystatin C mean (SD),mg/L	P
Gender					
Male	19	113.8 (47.37)	0.628	76.2 (22.26)	0.469
Female	17	105.9 (57.01)		69.0 (33.83)	
Age					
< 10 years	18	112.1 (52.75)	0.790	78.4 (28.24)	0.232
> 10 years	18	107.4 (51.77)		67.1 (27.62)	
Body Weight Status					

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Normal	15	116.1 (38.81)	0.788	80.0 (25.32)	0.378
Underweight	18	104.9 (64.13)		68.9 (30.89)	
Overweight	3	102.6 (18.89)		59.5 (21.32)	
Body Height Status					
Normal	20	116.6 (44.70)	0.397	74.1 (25.50)	0.760
Stunted	16	101.2 (59.43)		71.2 (31.88)	

Table 2 indicated the insignificant correlation between the estimation of GFR which was obtained from creatinine and cystatin C based equation according to CKD-EPI 2012 with gender, age, body weight, and body height.

Table 3: Difference in the stages of CKD based on the estimation of GFR between Creatinine and cystatin.

Stage of CKD	eGFR Creatinine	eGFR Cystatin C	RP	P
G1	26	9		
G2	5	19	3.373 (1.378-5.156)	0.001*
G3a+				
G3b	1	4	3.513(1.571-5.351)	0.001**
G4+				
G5	4	4	1.486(0.228-2.136)	0.063**

C. *chi-square test **fischer test.

Table 3 indicated the difference in the degree of CKD stages by comparing the estimation of GFR based on creatinine and cystatin C using CKD EPI equations as its indicators. This table also showed the significant difference statistically in stages of CKD which stated that the comparison among G1 stage (described as high or normal kidney function) compared with G2 stage (the mild decrease in kidney function) and G3a + G3b stage (medium decrease in kidney function) at P value < 0.05. Meanwhile, the comparison of eGFR based on creatine and cystatin C between G1 stage and G4+G5 stage was at P value >0.05 which was statistically in significant , thus it made cystatin C also can be a reliable marker for eGFR beside creatinine.

G1 stage which was compared with G2 stage had RP value of 3.373 which indicated that there were 3.373 times more found in G1 stage than that found in G2 stage when the eGFR was based on creatinine, compared with the eGFR based on cystatin C. This study was also indicated that it were 3.513 times cases found in G3a+G3b compared to G1 when the eGFR was based on creatine compared to cystatin C which considered as the sensitivity in assessing decreased renal function was better in cystatin C rather than creatinine. The ratio prevalence which was not far different was indicated by the estimation of GFR based on creatinine and cystatin C in G4 and G5 stages in which the decrease of renal function was already severe and even in end stage or failure condition.

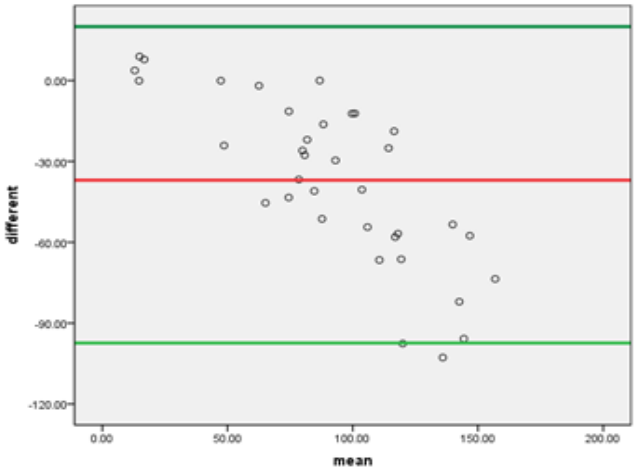
Table 4: Proportion between estimated GFR based on cystatin C and creatinin in differentiating normal and decreased renal function.

		eGFR Cystatin C			
		Normal	**Decreased**	**Total**	**P**
eGFR Creatinine	Normal	9 (25)	17 (47.2)	26 (72.2)	0.001*
	Decrease	0 (0)	10 (27.8)	10 (27.8)	
Total		9 (25)	27 (75)	36 (100)	

*McNemar Test

Table 4 indicated the proportion of GFR estimation based on creatinine and cystatin C in differentiating normal renal function from the decreased kidney function by using McNemar test at P value < 0.05 so that statistically there was significant difference in assessing kidney function by using eGFR between creatinine and cystatin C. Table 5 indicated the agreement between the eGFR based on creatinine and cystatin C.

Table 5: Agreement between eGFR based on Cystatin C and Creatinine using Blant-Altman analysis.



Discussion

Chronic Kidney Disease (CKD) is an important health problem throughout the world. Its high prevalence resulted in poor outcomes and high cost burden that made the change in paradigm of CKD management nowadays, where the campaign of early detection and prevention and integrated management from various fields are more encouraged than the follow up actions of CKD by renal replacement therapy [19].

CKD in children can also develop to be renal failure when its management is done inaccurately and late. CKD in children has a very significant effect in which death rate in children suffered from renal failure is estimated to be 30 times higher than that in child population in general [20]. Evaluation on renal function by assessing GFR is very important. A study conducted in the United States estimates that there is the decrease in renal failure in CKD patients from 3 to 5ml/min/1.73m2 each year which indicates that it is mostly possible that patients with renal failure might have suffered from CKD in the initial stage in their childhood and adolescence [20].

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One of the best strategy to improve CKD prognosis in children is by evaluating risk factors and detecting the decrease in kidney function so that the management of fluid and electrolyte balance, the adjustment dose of medicines in order to maintain kidney function and prevent it from toxicity, can be done immediately [20,21] GFR is the best index which describes kidney function completely. Accurate examination on GFR with exogenous marker can hardly be done in our centre so we did our study by comparing creatinine serum as referenced standard markers with cystatin C as the other potential endogenous marker in assessing estimated GFR (eGFR). Creatinine serum which has been used as the marker of GFR for more than 100 years is already known for its limitation [22]. Creatinine is considered as not sensitive marker to detect mild and medium decrease of renal function, also known as 'creatinine blind area' so that the over estimation of GFR usually occurs and make lots of under diagnosed cases [23]. This is in accordance with the result of this study in which the proportion of GFR estimation based on cystatin C and creatinine in CKD patients had significant difference in differentiating normal to decreased kidney function (GFR >90ml/min/1.73m2).

It was also found in this study that there was significant difference in the value of GFR estimation between creatinine and cystatin C in the CKD initial stage although it was not far different when it was compared at the severe stage. This significant difference occurs when G1 stage (normal kidney function) is compared with G2 stage and G3a+G3b (the decrease from mild to medium kidney function). This is in accordance with the previous study in Colombia in 2008 which indicated that cystatin C was more sensitive than creatinine in the initial stage of CKD [24]. A study with the same result in Malaysia in 2013 also revealed that cystatin C is significantly increased in stage G2 of CKD (the mild decrease in kidney function) compared with creatinine [25]. The similarity found between cystatin C and creatinine in severe stage of CKD may indicate that cystatin C could also be reliable marker for eGFR and moreover with better performance when it is used in the initial stage of CKD.

Other previous studies had often differentiated between these two markers. Another study conducted in India in 2014 which differentiated the examination of GFR estimation between creatinine and cystatin C by using gold standard 99Tc-DTPA also found that GFR estimation according to cystatin C had higher precision than creatinine (13.1 vs. 25.6mL/min/1.73m2) [13]. A study conducted in Colombia in 2008 also revealed that cystatin C was a very interesting option which could replace creatinine serum in diagnosing and monitoring renal function in children [24]. A meta-analysis study in 2013 which used CKD-EPI equation, as what had been done in this study found that cystatin C was more significant than creatinine in recognizing the advanced risk of CKD because it was closely related to GFR assessment and CKD classification [26].

The study conducted in Haji Adam Malik Hospital did not use any samples as control or gold standard so the accuracy could not be assessed, either its sensitivity or its specificity. It was also not a diagnostic study because it was only a conformance test by using referenced standard namely creatinine. In this study, we calculated the GFR estimation by using CKD-EPI equation in order to obtain a more equivalent comparison according to the recent recommendation.

Besides its insensitivity, creatinine is also considered having inconstant value and is influenced by other factors like age, gender and muscle mass, dieting, and so on. Cystatin C is considered free from these influences, including by inflammation and malignancy [27]. A study which was published in Turkey in 2015, using control to assess correlation of the factors with GFR estimation according to creatinine and cystatin C found that creatinine value had significant correlation with age, body height, and body mass index (BMI), while cystatin C did not [28]. In this study, we found that age, gender, body height, and body weight had insignificant correlation with the value of both GFR estimation based on creatinine and cystanin C.

Besides the excellences of cystatin C as marker in assessing GFR estimation, cystatin C also has its own limitation. Some studies also point out that there is the correlation of cystatin C level with patients' thyroid status and the use of steroid [29]. In this study, even though we asked the patients about the status of using steroid, we did not analyze the correlation of using steroid with cystatin C level. The examination on thyroid hormone was also not done and there was no assessment on thyroid hormone status in our samples. It is, therefore, necessary to do further study on various factors which can influence the cystatin C as marker of eGFR since nephrotic syndrome with the treating of steroid in such long term which can affect the patients' thyroid status occurs in most of CKD cases.

With all its excellences in assessing GFR estimation compared with creatinine, cystatin C still in the hard way to substitute creatinine which has been used widely in all over the world. This is also related to the factor of high cost in which the cost of examination on cystatin C takes about 5 to 6 times compared with creatinine, and the variety of standardization in various places and countries. A study conducted in Korea in 2011 revealed that the mild increase in cystatin C serum with normal creatinine value did not have any signifcant difference clinically [30]. This can probably become the consideration to do the examination on cystatin C in CKD cases prior to patients who are susceptible to undergoing the decrease in kidney function.

Further study on the equation used in assessing GFR estimation according to creatinine and cystatin C is still needed. Another study in Switzerland in 2013 on the comparison between CKD-EPI equation and Schwatz equation which used insulin gold standard found that CKD-EPI equation was not considered better than Schwartz equation in assessing GFR estimation [31]. Unfortunately, we did not compare Schwartz equation with CKD-EPI equation in this study. The other limitations of this study were the small population recruited as samples and no GFR

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examination by using gold standard or exogenous markers due to the unavailability of facility in the study area.

Conclusion

There is a significant difference between creatinine and cystatin C for estimation of GFR in early stage of CKD in children. This can probably become the consideration to do the examination on cystatin C in CKD cases prior to patients who are susceptible to undergoing the decrease in kidney function.

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