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혈청 Cystatin C와 크레아티닌에 근거한 사구체 여과율의 비교

신호식 • 정연순 • 임학

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Glomerular Filtration Rate by Cystatin C-Based Prediction Equations Compared with Serum Creatinine Based GFR in Healthy Young Korean Men

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---- Abstract

Background: In recent years, cystatin C (CysC) was proposed as a new marker for the glomerular filtration rate (GFR) due to a constant serum level. The present study analyzes whether creatinine based GFR prediction equations might be replaced by simple prediction equations based on serum concentrations of CysC in healthy young Korean men. **Methods**: We studied 145 apparently healthy young Korean men aged 19-29 years who visited The Armed Forces Yangju Hospital (Gyeonggi Province, Repulic of Korea) for health check from November 2008 to January 2009. Creatinine-based GFR was estimated by the formula of modified MDRD, Crockcroft Gault (CG). CysC-based GFR was estimated by the formula of correlations between GFR estimating formulae based upon serum CysC and serum creatinine.

Results : Among CysC based GFR, Hoek's GFR is most similar with CG GFR and abbreviated MDRD GFR. Significant correlations were noted between CysC based GFR and creatinine based GFR.

Conclusion: Creatinine based GFR prediction equations for healthy young Korean men might be replaced by simple prediction equations based on serum concentrations of CysC (especially Hoek' equation).

Key words : Cystatin C, Creatinine, Glomerular filtration rate

Introduction

The GFR is the most widely used global index of renal function. Determination of GFR with high accuracy requires the use of invasive techniques based on measuring the plasma clearance rate of injected substances that are exclusively excreted via glomerular filtration, e.g., inulin, ⁵¹Cr-EDTA, ^{99m}Tc-diethylenetriaminepentaacetic acid, or radiographic contrast media such as ¹²⁵Iiothalamate and iohexol. These procedures are laborious, time-consuming for

a routine clinical use and not entirely free of risk for the patient. There, measurements of the endogenous markers are in common practice.¹⁾

The most commonly used endogenous marker is creatinine. However, creatinine production depends on muscle mass and is age and sex related. As a result, a wide reference range is found.²⁾ The most widely accepted and used GFR prediction equations for adults are that proposed by Cockcroft and Gault³⁾ and the Modification of Diet in Renal Disease (MDRD) equations.⁴⁾

CysC, a 132-amino acid, 13-kDa cysteine proteinase inhibitor, has been suggested to be a better marker for GFR than creatinine because believed to be produced at a constant rate by all nucleated human cells, and eliminated

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exclusively by glomerular filtration.^{5,6)} And plasma CysC values are reported to be unaffected by age, body weight, diet, medications, or pathologies such as inflammation and cancer.⁷⁾ One limitation of using CysC as a GFR marker is that there is no international standard's version formula transforming CysC expressed as mg/dL to GFR expressed as mL/min. The present study analyzes whether creatinine based GFR prediction equations might be replaced by simple prediction equations based on plasma concentrations of CysC in healthy young Korean men.

Materials and Methods

Subjects

We studied 145 apparently healthy young Korean men aged 19-29 years who visited The Armed Forces Yangju Hospital (Gyeonggi Province, Repulic of Korea) for health check from November 2008 to January 2009. All of the subjects were healthy and had no renal disorders. The study was reviewed and approved by the Ethics Committee of The Armed Forces Yangju Hospital. Informed consent was provided by patients before participating in the study.

The subjects were selected for this study on the basis of the following criteria:

(i) No history and signs/symptoms of any renal or non-renal disease as well as hypertension during the past six months

(ii) The subjects who treated with drugs that may influence the renal function or serum CysC concentrations (i.e., anti-hypertensive, diuretics, anti-inflammatory agents, anticonvulsants, hypoglycemic agents, anti-cancer or antiviral drugs and antibiotics) were excluded.

(iii) Normal dipstick urine test, and normal creatinine (\leq 1.3 mg/dL)

Serum creatinine and cystatin C

The serum creatinine level was measured using a compensated calibrator for the Jaffe method, which was rate-blanked on a Hitachi 747 Auto analyzer (Hitachi, Japan). The serum CysC was measured in a particle enhanced immunonephelometry method, on a BN II

nephelometer (Dade Behring, Germany). In this assay, polystyrene beads coated with rabbit antibodies to CysC agglutinate when mixed with samples containing CysC.⁸⁾ The intensity of the scattered light in the nephelometer depends on the concentration of CysC in the sample. This concentration is determined by comparison with dilutions of a calibrator. All serum samples were analyzed within 3 days or stored frozen until analysis.

Body index

We used the data of patient's height and weight registered on medical record to yield the value of body index.⁹⁾ : Body surface area (BSA) was calculated using the following formulae.

 $[{\text{height (cm) x weight(kg)}}/3600]^{1/2}$

Body mass index (BMI) = Body weight $(kg)/height^2 (m^2)$

Glomerular Filtration Rate by creatinine-Based Prediction Equations

CG GFR = [140-age(years)] x weight (Kg) / [0.815 x]serum creatinine (mg/dL)³⁾ Abbreviated MDRD GFR = 186 x [Scr] ^{-1.154} x [Age] ^{-0.203} x [0.742 if patient is female]¹⁰⁾

Glomerular Filtration Rate by CysC-Based Prediction Equations

Larsson' GFR ¹¹⁾ = 99.43 x CysC^{1.5837} Hoek's GFR ²⁾ = (80.35 / CysC)-4.32 Filler's GFR ¹²⁾ = 91.62 x CysC^{1.123} Grubb's GFR ¹⁾ = 84.69 x CysC^{1.680} x 1.384 Le Bricon GFR ¹³⁾ = (78 / CysC) + 4 Orebro-cyst (DAKO) GFR ¹⁴⁾ = (119 / CysC)-33 Orebro-cyst (Gentian) GFR ¹⁴⁾ = (100 / CysC)-14

Statistical analysis

The results are presented as the mean \pm SD. We used Pearson's correlation coefficient to evaluate the relationship between the parameters. Linear regression analysis was performed to evaluated correlations between GFR estimating formulae based upon serum CysC with serum creatinine. The results were considered significant when the P value was below 0.05. A statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 152 healthy men were screened of whom 7 were excluded because of underlying diabetes mellitus, hypertension or raised urine levels of protein. The remaining 145 subjects (all males), with a mean age of 21.6 \pm 1.4 years (range of age 19-29), who fulfilled the required criteria, were finally selected. The clinical characteristics of the subjects were summarized in Table 1.

Table 1. Clinical Characteristics of Subjects

	Mean \pm SD	Range
No. of subjects	145	
Age (years)	21.6 ± 1.4	19 - 29
Height (cm)	174.6 ± 0.0	162 -193
Weight (kg)	69.5 ± 10.2	51 - 104
BMI (kg/m ²)	22.7 ± 2.9	17.6 - 32.0
BSA (m ²)	1.83 ± 0.14	1.55 - 2.29
Lean body mass (kg)	55.8 ± 5.6	44.5 - 73.0
BUN (mg/dL)	12.7 ± 3.1	5.9 - 22.9
Cr (mg/dL)	1.03 ± 0.12	0.8 - 1.3
Cystatin C (mg/L)	0.76 ± 0.09	0.60 - 1.25
WBC (/mm ³)	6582 ± 1761	2820 - 13590
Hb (g/dL)	15.1 ± 0.9	12.4 - 18.4
Platelet (/mm ³)	238675 ± 54767	119000 - 448000
Na (mEq/L)	143 ± 1	134 - 150
K (mEq/L)	4.4 ± 0.3	3.4 - 5.6
CI (mEq/L)	103.9 ± 1.5	99 - 108
Protein (g/dL)	7.3 ± 0.4	6.5 - 8.5
Albumin (g/dL)	4.5 ± 0.2	3.6 - 5.2
Glucose (mg/dL)	91 ± 19	70 - 175
Total cholesterol (mg/dL)	166 ± 30	113 - 336
LDL (mg/dL)	91 ± 26	44 - 254
HDL (mg/dL)	51 ± 12	24 - 105
TG (mg/dL)	108 ± 85	15 - 530
Uric acid (mg/dL)	5.6 ± 1.2	0.6 - 9.4

The determination of CysC values in serum showed a Gaussian distribution (P < 0.05). The analysis of CysC data established a reference interval for young Korean men of 0.60–1.25 mg/L (0.76 ± 0.09 mg/L, 2 SD). Table 2 showed mean values of CysC & creatinine based GFR of subjects. Among CysC based GFR, Hoek's GFR (102 ± 12 mL/min/1.73 m², range 78-140) is most similar with CG GFR (105 ± 14, 62-130) and abbreviated MDRD GFR

 $(97 \pm 14, 62-130).$

Table 2. Mean values of CysC & creatinine based GFR of subjects

Calculated GFR (mL/min/1.73m ²)	Mean ± SD	Range	
Cockcroft-Gault GFR	105 ± 14	78 -140	
abbreviated MDRD GFR	97 ± 14	62 - 130	
Larsson GFR	156 ± 28	69 - 223	
Hoek GFR	102 ± 12	59 - 129	
Filler GFR	126 ± 16	71 - 162	
Grubb GFR	136 ± 26	58 - 199	
LeBricon GFR	107 ± 12	66 - 134	
Orebro-cyst DAKO GFR	124 ± 18	62 - 165	
Orebro-cyst Gentian GFR	118 ± 15	66 - 152	

CysC significantly correlated with creatinine, CG GFR and abbreviated MDRD GFR (P = 0.0001, 0.002 and 0.001, correlation coefficient = 0.302, -0.257 and -0.267, respectively) (Table 3).

Table 3. Pearson correlation coefficients between Cystatin C, creatinine and creatinine based GFR

	R	P value
Creatinine	0.302	0.0001
Cockcroft-Gault GFR	-0.257	0.002
abbreviated MDRD GFR	-0.267	0.001

Serum creatinine significantly with CysC based GFR. Creatinine significantly correlated with Hoek's CysC based GFR (P = 0.0001, correlation coefficient = -0.335) (Table 4).

Table 4. Pearson correlation coefficients between creatinine and CysC/creatinine based GFR

	R	P value
Cockcroft-Gault GFR	-0.857	0.0001
abbreviated MDRD GFR	-0.959	0.0001
Larsson GFR	-0.341	0.0001
Hoek GFR	-0.335	0.0001
Filler GFR	-0.335	0.0001
Grubb GFR	-0.343	0.0001
LeBricon GFR	-0.335	0.0001
Orebro-cyst DAKO GFR	-0.335	0.0001
Orebro-cyst Gentian GFR	-0.335	0.0001

Table 5. Correlation between creatinine based GFR and cystatin C based GFR

Variables	Crockroft Gault GFR		abbreviated MDRD GFR	
	R	P value	R	P value
Larsson GFR	0.289	0.0001	0.309	0.0001
Hoek GFR	0.281	0.001	0.302	0.0001
Filler GFR	0.281	0.001	0.302	0.0001
Grubb GFR	0.285	0.001	0.312	0.0001
LeBricon GFR	0.281	0.001	0.302	0.0001
Orebro-cyst DAKO GFR	0.281	0.001	0.302	0.0001
Orebro-cyst Gentian GFR	0.281	0.001	0.302	0.0001

CysC based GFR significantly correlated with creatinine based GFR (Table 5). The relationship between CysC and CG GFR was estimated from a simple linear regression as follows: CG GFR (mL/min/1.73m²) = -38.5 CysC + 135.1 (r^2 = 0.066, F =10.141, and P = 0.002). (Fig. 1) The relationship between CysC and abbreviated MDRD GFR was estimated from a simple linear regression as follows: abbreviated MDRD GFR (mL/min/1.73m²) = -40.7 CysC + 128.9 (r^2 = 0.071, F = 10.972, and P = 0.001). (Fig. 2) The relationship between CG GFR and Hoek's CysC based GFR was estimated from a simple linear regression as follows: Hoek's CysC based GFR (mL/min/1.73m²) = 0.25 CG GFR + 75.9 (r^2 = 0.079, F = 12.249, and P = 0.001). (Fig. 3) The relationship between abbreviated MDRD GFR and Hoek's CysC based GFR was estimated from a simple linear regression as follows: Hoek's CysC based GFR was estimated from a simple linear regression as follows: Hoek's CysC based GFR was estimated from a simple linear regression as follows: Hoek's CysC based GFR was estimated from a simple linear regression as follows: Hoek's CysC based GFR was estimated from a simple linear regression as follows: Hoek's CysC based GFR was estimated from a simple linear regression as follows: Hoek's CysC based GFR was estimated from a simple linear regression as follows: Hoek's CysC based GFR (mL/min/1.73m²) = 0.26 abbreviated MDRD GFR + 76.5 (r^2 = 0.091, F = 14.337, and P = 0.0001). (Fig. 4)



Fig. 1. Correlation between Crockroft Gault GFR and serum cystatin C. Linear regression analysis gave y = -38.5x + 135.1, $r^2 = 0.066$, P = 0.002



Fig. 2. Correlation between abbreviated MDRD GFR and serum cystatin C. Linear regression analysis gave y = -40.7x + 128.9, $r^2 = 0.071$, P = 0.001



Fig. 3. Correlation between Hoek's cystatin C based GFR and serum creatinine. Linear regression analysis gave y = 0.25x + 75.9, $r^2 = 0.079$, P = 0.001



Fig. 4. Correlation between Hoek's cystatin C based GFR and serum creatinine. Linear regression analysis gave y = 0.26x + 76.5, $r^2 = 0.091$, P = 0.0001

Discussion

The present study analyzes whether creatinine based GFR prediction equations might be replaced by simple prediction equations based on plasma concentrations of CysC in healthy young Korean men. Creatinine based GFR prediction equations (i.e. CG and abbreviated MDRD GFR equation) might be replaced by simple prediction equations based on plasma concentrations of CysC (especially Hoek' equation) in healthy young Korean men.

In South Korea, military service is compulsory for all healthy young men, and hence, the army population reflects the general population. Therefore, the results of this study might represent CysC and creatinine based GFR in healthy young Korean men. Furthermore, the study population comprised subjects of only one gender and with relatively less age variation than the general population. This enabled an age- and gender-independent evaluation of CysC and creatinine based GFR in young Korean men.

CysC is an endogenous, 13 kilodalton protein filtered by the glomeruli and reabsorbed and catabolized by the tubular epithelial cells with only small amounts excreted in the urine, and reported to be generated at a relatively constant rate irrespective of muscle mass.¹⁵⁾ Thus, it was anticipated that CysC would provide a better estimate of GFR than estimating equations based on serum creatinin.¹⁵⁾ And comparative studies have shown that CysC is more sensitive than serum creatinine for detecting slight changes in renal function.^{5,16)}

Previous studies have shown a wide variability in eGFR for the same level of CysC.¹⁷⁾ These differences may be related to the variation among populations, or to differences among assays or GFR measurement methods. The high level of variation in the CysC assay is beginning to be recognized, and standardization and calibration of clinical laboratories will be important to obtain accurate GFR estimation using cystatin C.¹⁸⁾

It has been clearly demonstrated that the selection of persons used for constructing prediction equations for GFR significantly influences the prediction equations obtained.¹⁹⁾ The MDRD equation was derived from data from a cohort of persons with chronic kidney disease and did not include healthy persons.¹⁹⁾ This might impair its diagnostic performance for populations including a high proportion of healthy persons, e.g., the population studied in the present investigation. GFR estimating equations using CysC have the promise to provide more accurate estimates of GFR than equations using serum creatinine. Implementation of these equations in routine clinical practice requires standardization of the CysC assay, further investigation of the factors other than GFR that influence the level of CysC, and availability of wide-spread and cost-effective assays for additional markers. At the current time, the equations used here may provide more accurate estimates in people in whom estimates based on serum creatinine are likely to be inaccurate due to conditions affecting muscle mass or diet or to estimate change in GFR over time in

people with changing muscle mass or diet.

Several formulae for estimating GFR based upon CysC determination have been proposed.^{1,2,11,13,14,20)} Since there is no international standard for CysC, these GFR estimates vary with the analytical method and the formula the local laboratory uses to calculate the GFR from the analysis result.²¹⁾ And, to our knowledge, no studies suggesting prediction equations for relative GFR based on CysC and comparing prediction equations for CG and abbreviated MDRD GFR in healthy young Korean men. Because the serum CysC concentration, in contrast to that of serum creatinine, has been described as virtually constant among healthy individuals¹⁾, we used the 1-parameter cystatin C prediction equation for prediction of GFR of all 145 subjects (19-29 years of age) investigated in the present study. This study shows that CysC level can be used in a simple formula (especially, Hoek's equation) to give a significantly more accurate and precise quantitative estimate of GFR than obtained by CG & abbreviated MDRD.

Although the results of the present investigation suggest that simple CysC based prediction equations might offer advantages compared with creatinine based prediction equations, it should be emphasized that CysC based prediction equations cannot replace the use of gold standard procedures for determination of GFR because the diagnostic performance of CysC based prediction equations is not perfect, particularly in some clinical situations, e.g., patients treated with large doses of corticosteroids²²⁾ or patients with thyroid dysfunction²³⁾, and also because the diagnostic performance of CysC based equations has not been tested in all relevant clinical situations. In our study, all of the subjects were healthy and had no renal and thyroid disorders. And the subjects who treated with drugs that may influence the renal function or CysC serum concentrations (i.e., anti-hypertensive, diuretics, anti-inflammatory agents, anticonvulsants, hypoglycemic agents, corticosteroids, anti-cancer or antiviral drugs and antibiotics) were excluded. Another point of concern about the applicability of CysC for the assessment of GFR is the large intra-individual variation observed for this protein. In combination with a much higher variability than achieved for creatinine, this results in a critical difference between

two consecutive observations much larger than for plasma creatinine. This observation was made in healthy volunteers.²⁴⁾ However, the use of CysC based prediction equations may reduce the need to perform invasive determinations of GFR and may allow a more precise selection of patients requiring gold standard procedures. From Medline research, a total of 7 studies that provide reference interval data for male populations using the nephelometric immunoassay were reviewed. Our male population reference interval established in the Behring assay was very similar among studies (range 0.48 mg/dL to 1.12 mg/dL).^{20,25-30)} Because of this, our CysC value was used as reference values of healthy young Korean men.

There are several limitations to this analysis. First, our study included only men and that the subjects were all young (19-29 years). Second, we did not use exogenous substances of gold standard for GFR (i.e. ¹²⁵I-labelled iothalamate and ¹³¹I-labelled hippuran).

In conclusion, creatinine based GFR prediction equations (i.e. CG and abbreviated MDRD GFR equation) for healthy young Korean men might be replaced by simple prediction equations based on plasma concentrations of CysC (especially Hoek' equation). A detailed study including male and female Korean is required to develop Cystatin C-Based Prediction Equations for Korean adults

Conflict of Interest Statement

We have no relation with Hitachi company (Japan) and Dade Behring company (Germany) and we have not received any support from that incorporation. The views, options, and/or findings contained in this article are those of the authors and do not reflect the official policy or position of the Ministry of National Defense or the Government of South Korea.

국문초록

배경: 혈청 cystatin C는 외부 요인에 영향을 받지 않고 일정한 값을 유지하므로 사구체 여과율에 대한 새로운 표지자로 제시되고 있다. 본 연구는 젊은 성인 남성에서 혈청 Cystatin C와 크레아티닌에 근거한 사구체 여과율의 비교

cystatin C에 근거한 사구체 여과율이 혈청 크레아티닌에 의한 사구체 여과율을 대체할 수 있는지 조사하였다.

방법 : 2008년11월부터 2009년1월까지 병원을 방문한 평 균 연령 21세의 젊은 성인남성 145명을 대상으로 하였다. Cystatin C에 근거한 사구체 여과율은 Larsson, Hoek, Filler, Grubb, Le Bricon, Orebro-cyst (DAKO), Orebro-cyst (Gentian) 공식을 이용하였고 혈청 크레아티 닌에 근거한 사구체 여과율은 변형된 MDRD, Crockcroft Gault 공식을 이용하여 산출하였다. Cystatin C에 근거한 사구체 여과율과 혈청 크레아티닌에 근거한 사구체 여과 율은 선형 회귀분석을 통해서 연관 관계를 확인하였다

결과 : Cystatin C에 근거한 사구체 여과율 산출 공식중에 서 Hoek 공식에 의한 사구체 여과율이 혈청 크레아티닌 에 근거한 사구체 여과율과 의미있는 상관관계를 보였 다.

결론 : 젊은 성인 남성에서 Cystatin C에 근거한 사구체 여과율은 혈청 크레아티닌에 의한 사구체 여과율을 대체 할 수 있을 것으로 생각된다.

중심단어 : Cystatin C, 크레아티닌, 사구체 여과율

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