Renal function in community-dwelling frail elderly. Comparison between measured and predicted glomerular filtration rate in the elderly and proposal for a new cystatin C-based prediction equation

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ABSTRACT. ***Background and aims:*** *There is a great need to evaluate renal function regularly in elderly people. This study aimed at analyzing renal function in stable, community-dwelling elderly people of 75 years and over, to compare measured and predicted glomerular filtration rates (GFR) and to develop an accurate prediction equation for this age group.* ***Methods:*** *Forty-five ambulatory elderly people in stable health in ordinary living were randomly selected into four age-classes, aged 75-95. Demographic data, personal activities of daily living, continuous drug prescriptions, body composition, blood pressure and blood chemistry were analysed. GFR was measured as Iohexol clearance based on three time-points 3, 4 and 7 hours after Iohexol injection.* ***Results:*** *Mean GFR was well preserved in all four age-classes. The GFR range was 18-83 mL/min and declined with age. The Cockcroft-Gault prediction equation systematically underestimated measured GFR. A new 'GFR_A' prediction equation is presented, based on the inverse of serum cystatin C and independent of gender, body surface area, body weight, lean body mass or serum creatinine. The proposed equation underestimated measured GFR with a mean of only 0.1 mL/min, had better precision compared with the Cockcroft-Gault equation, and was evaluated by the method of cross-validation.* ***Conclusions:*** *GFR exhibits extensive heterogeneity in frail, community-dwelling elderly people. The proposed GFR_A was clearly more precise than the Cockcroft-Gault prediction equation in the study group. However, it needs to be validated in a larger population of elderly subjects, including more individuals in stable health with substantially reduced renal function in whom GFR is measured by a reference method with adequate sampling time.*

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INTRODUCTION

With increasing age there is a physiological decline in renal as well as heart and lung functions (1, 2). Inter-individual variations in these physiological processes are large. In addition, the negative effects of various diseases such as atherosclerosis, diabetes mellitus and heart failure are added to the age-related loss of renal function to varying extent. When renal function has decreased to about one-third of normal, secondary events appear, such as disturbed calcium-phosphate balance, secondary hyperparathyroidism and secondary anemia. At this level of renal function loss, pharmacokinetics are also deeply affected. When caring for elderly patients, knowledge of their renal function is thus essential.

In contrast to the function of other organs, renal function can be quite well estimated. The "golden standard" is measurement of inulin clearance by estimating glomerular filtration rate (GFR) and PAH clearance by estimating renal blood flow (i.e., GFR plus tubular secretion). In clinical practice, measurement of GFR is usually sufficient, since tubular function generally is in balance with GFR. More easily performed methods for assessment of GFR have been developed, such as ^{51}Cr-EDTA clearance and later Iohexol clearance (3, 4). However, they are still not simple or cheap enough for daily routine use. There is thus a great need for valid endogenous filtration markers to predict GFR.

Endogenous creatinine clearance ($GFR_{Creatinine}$) gives an estimate of GFR with the addition of a smaller component

Key words: Community-dwelling, elderly, glomerular filtration rate, prediction equation.

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of tubular secretion. Thus, $GFR_{Creatinine}$ overestimates GFR already at normal renal function, and even more so with progressing renal insufficiency (5). The method requires quantitative urinary collection, which may be difficult to perform, particularly in the elderly. Also, the serum creatinine level is related to the irreversible conversion from creatine to creatinine in skeletal muscle and, to some extent, to creatinine in cooked meat in the diet. Muscle mass falls with age at roughly the same rate as GFR (6) and, with reduced muscle mass, a normal or slightly elevated serum creatinine value may still reflect a substantial reduction in GFR.

Based on serum creatinine values, more than 25 different prediction equations have been developed to improve GFR assessment, and several reviews have been published (7, 8). Most of the formulas were created to estimate creatinine clearance, but not GFR, and most of them were based on populations with renal diseases (9). The most frequently used equation for estimating GFR in adults is the Cockcroft-Gault equation (GFR_{CG}) of 1976, which includes four variables; serum creatinine, age, body-weight, and gender, but which has not been standardized to body surface (10). This equation was originally developed in 249 adult male inpatients aged 18-92, of which 24% were 70 years and over. A recent study in healthy elderly persons aged 71-110 years found that the prediction equations of Cockcroft-Gault and Levy had a similar correlation coefficient (≈0.50) with GFR measured as Iohexol clearance (11).

There is accumulating evidence that serum cystatin C is superior to serum creatinine as an endogenous marker of GFR (8, 12). Human cystatin C is a Mr13-kD, 120-amino acid cystein protease inhibitor, constitutively and constantly produced by all types of nucleated cells. It is freely filtered by the glomeruli, reabsorbed, and fully metabolized in the proximal renal tubules (8). Unlike serum creatinine, serum cystatin C has been shown to be independent of age, gender, body weight, height, and diet. There is also an apparent lack of influence of medical conditions (for example, inflammation or malignancy; see also *Discussion*) on serum cystatin C, as well as little analytical interference (8).

The aim of the present study was i) to compare GFR predicted by the Cockcroft-Gault equation with meaured GFR, and ii) to use multivariate regression analysis to develop a more accurate prediction equation validated against direct measurement of GFR in a randomly selected community-dwelling elderly population aged 75 years and over.

MATERIALS AND METHODS

Selection of test subjects

In the summer of 2002, a questionnaire of eight questions regarding various aspects of nutrition and physical activity was distributed by regular mail to all 6197 community-dwelling individuals 75 years and older living in Solna, a suburb of Stockholm, Sweden. Without a reminder, the response rate was 49.7%. A summary report in Swedish has been published on our homepage (13). Of the responders, a total of 1721 individuals (56%) declared interest in participating in future research projects regarding nutrition and physical function in the elderly. From this group we subdivided all subjects into four age-classes, 75-79, 80-84, 85-89 and >90 years, and according to gender, and listed them by their social security number, which in Sweden is based on date of birth. According to available research resources, we decided to recruit 44 individuals, equally distributed by gender and the four age-classes. From the total number of men and women in each age-class, we randomly selected every n-th individual per class to offer participation. For example: in the age-class >90 years, there was a total of 24 men and 67 women and thus, every 5^{th} man and every 13^{th} woman were selected and offered participation by mail. If a selected individual declined participation, the next person in younger age order in the respective age and gender group was invited, until all age-classes were filled.

In order to include only subjects in stable health and to ensure active participation in the investigation, we applied the following four exclusion criteria: cognitive dysfunction scoring <7/9 on a 6-item cognitive screening test (14); use of wheel chair; ongoing renal dialysis, and admission to hospital within the past two months. We also excluded 100 individuals who had previously participated in a randomized controlled treatment trial of nutrition and physical activity in our research unit (15).

Examinations

All examinations were performed on an outpatient basis at our elderly research unit in Solna. Those who had accepted to participate were contacted by telephone for a structured interview. Selected subjects received a detailed questionnaire by mail, focusing on general health issues including ongoing drug treatment.

Body weight was measured with the participants, dressed in underwear, to the nearest 0.1 kg on a digital chair scale (Umedico SV-600, Rosersberg, Sweden). The body mass index (BMI) was calculated by dividing the body weight (kg) by $height^2$ (m). Personal activities of daily living (pADL) were estimated with the Swedish Functional Independence Measure (FIM) form (16).

Four skin folds were measured with a Harpenden caliper (British Indicators, Bedfordshire, UK) (17) over biceps, triceps, subscapular and crista iliaca on the left side, using the mean of three measurements to the nearest 0.1 mm from each location. Body density and fat mass were calculated from the sum of these four skin folds by prediction equations (18, 19). Lean body mass was calculated as body weight minus fat mass.

Arterial blood pressure was measured in the left arm in a sitting position on a validated digital blood pressure monitor UA-767 (A&D Medical, Tokyo, Japan). Mean arterial blood pressure was calculated by adding diastolic blood pressure + 1/3 of pulse pressure (20).

Laboratory testing (S=serum)

Fasting venous serum samples were analysed at the Department of Clinical Chemistry, Karolinska University Hospital, Stockholm. S-Creatinine was measured using the routine Jaffé method of the laboratory with a reference interval <110 µmol/L. S-Cystatin C was analyzed by the N Latex cystatin C assay (Dade Behring Inc, Marburg, Germany) on a BN ProSpec instrument (Dade Behring). The reference interval in our lab is <1.6 mg/L for men and <1.3 mg/L for women with a reproducibility between runs of 2.8 and 3%.

GFR was measured as a 3-point Iohexol clearance as follows: 5 mL of Iohexol (Omnipaque®, Amersham Health), 300 mg iodine/mL corresponding to 647 mg Iohexol (same dose to all test subjects, independent of body weight) was injected into an antecubital vein in the fasting state between 8 and 9 a.m. To obtain the exact amount of injected Iohexol, the syringe was weighed to two decimal points before and after the injection on a precision scale (Sartorius BP310DS, Germany). After injection, the needle was flushed with 20 mL NaCl. Three serum samples were drawn exactly 3, 4 and 7 hours after the injection. Blood samples were immediately centrifuged (Hettich Zentrifuge Universal 1200, Tuttlingen, Germany) at room temperature at 3200 rev/min for 10 minutes, the serum was separated, chilled on ice, and immediately transported to the laboratory for analysis. For each test person, a serum sample was frozen at -70°C. S-Iohexol was measured by HPLC, and the three analysis points were used to establish an elimination function. After adjusting for the distribution volume for men (166 × weight in kg + 2490) and women (95 × weight + 6107 for women) (21) and then a further correction by division by an empirically found function (0.991 minus volume × 0.00122) (22, 23), the absolute GFR was obtained. GFR was expressed both in absolute values (mL/min) and after normalization to body surface (mL/min/1.73 m^2) (24). The total variation in GFR measured by Iohexol clearance has been reported to be about 11% (25).

All participants gave their written informed consent to participate in the study. No financial compensation was provided. The study was approved by the research ethics committee at Karolinska Institutet in Stockholm.

Statistical analysis

Analyses of differences in baseline characteristics between the four age groups were investigated by an ANOVA for continuous data with normal distribution. Pair-wise

Table 1 - *Baseline characteristics for four age groups. Statistically significant differences in bold (p<0.05).*

Baseline characteristics	75-79 years (n=10, 5 males)				80-84 years (n=13, 7 males)				85-89 years (n=10, 4 males)				>90 years (n=12, 6 males)			
	Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range
Age (yrs)	77.4	1.2	77.5	76-79	81.9	1.3	82	80-84	87	0.67	87	86-88	92.7	2	91.5	91-96
Personal ADL (FIM)			90	81-91			91	84-91			87	81-90			**87***	**77-91**
Body weight (kg)	79.1	11.9	78.7	60-99.5	63.2	10.7	63	46-76.5	68	10.8	65	54.8-85.1	**66****	**8.2**	**64.5**	**52.3-81.9**
Body mass index (kg/m^2)	**27.3**§**	**3.1**	**26.6**	**23.9-32.1**	22.7	2.2	22	18.8-26.5	25.2	4	24.3	19.0-32.0	23.3	1.6	23.6	20.7-25.5
Lean body mass (kg)	48.2	9.4	47.1	36.1-62.6	43.7	8.8	48	32.4-56.0	43.4	7.2	41.4	35.2-58.0	42.5	7.3	41.4	33.7-53.2
Systolic blood pressure (mmHg)	157	29	152	125-215	164	18	165	124-186	163	22	161	130-200	161	30	164	105-205
Diastlic blood pressure	86	14	85	65-114	84	15	80	60-115	91	12	87	75-110	82	16	81	60-110
Mean blood pressure (mmHg)	110	16	110	90-139	111	12	108	94-135	115	13	113	97-139	108	20	111	75-138
Pulse pressure	70	26	68	41-130	80	23	85	44-120	73	20	73	44-111	78	20	83	45-120
Heart frequency (beats/min)	74	9	77	63-85	72	13	68	58-106	77	8	77	63-90	69	13	69	50-98
Continuously taken drugs (number)	2	1	2	0-4	4	3	3	0-11	3	3	1	0-9	6	5	5	0-17
S-Creatinine (µmol/l)	73	10	74	56-88	89	16	95	51-114	122	134	82	57-499	111	50	88	66-218
S-Urea (mmol/l)	5.5	1.2	5.4	4-7.6	6.6	1.9	6.4	3.8-9.5	7.9	4.1	7	4.1-18.4	10.2	6.6	8.4	4.7-27.4
$GFR_{Iohexol}$ (ml/min)	**70.1**	**8.3**	**71**	**54-83**	56.7	9.9	52	44-73	59.1	17.7	63	18-82	**45**	**12.4**	**39.5**	**29-62**
$GFR_{Iohexol}$ (ml/min/1.73 m^2)	**63.2**†**	**9**	**65**	**50-77**	58.5	13.4	56	44-85	58.3	17	61,5	17-79	**45.1**†**	**14**	**41.5**	**26-68**
GFR_{CG} (ml/min)	79.4†	14.1	80.5	60-99	47.4	11.1	45.6	29-68	47.1	17.4	47.2	9-68	36‡	11.5	39.9	19-48
S-Cystatin C (mg/l) (n=44)	0.94	0.2	0.89	0.67-1.2	1.11	0.2	1.18	0.83-1.46	1.32	0.7	1.13	0.79-3.19	1.55	0.5	1.35	0.92-2.37

*significant difference compared with age group 80-84; **significant difference compared with age groups 75-79 and 80-84; §significant difference compared with age groups 80-84 and >90; †significant difference compared with age groups 80-84, 85-89 and >90; ‡significant difference compared with age group 75-79; ADL: Activities of daily living; FIM: Function independence measure; S: Serum.

Table 2 - *Continuously taken medicinal drug prescriptions in four age groups classified according to WHO Anatomical Therapeutic Chemical (ATC) code for each drug group.*

	75-79 years	80-84 years	85-89 years	>90 years
A02B: Anti-ulcer drugs			**1**	**3**
Proton-pump inhibitors			1	1
Histamine H2-receptor blockers				1
Surface active prostaglandins				1
A06: Laxatives				**2**
Lactilol				1
Na-picosulphate				1
A10B: Oral antidiabetic drugs	**2**	**1**		**2**
Glibenclamide		1		2
Glimiperid	1			
Metphormin	1			
A11: Vitamins	**2**	**3**	**6**	**8**
Vit B1				1
Vit B12		1	3	3
Folic acid		1		2
Comb. Vit B12, folate, Vit B6	1		2	
Vit C				1
Vit D3				
Vit K		1		
Vit E			1	1
Multivitamins	1			
A12: Minerals		**1**	**1**	**7**
Kalium (K)				3
Calcium (Ca)		1		2
Magnesium (Mg)				1
Iron (Fe)			1	1
A12A: Combination vitamins/minerals		**3**		
Comb. Vit. D3/calcium		3		
B01A: Platelet-antiaggregating drugs	**2**	**5**	**4**	**4**
Acetyl-salicylic acid (ASA)	2	4	3	4
Dipyridamol		1	1	
B01A: Anticoagulating drugs		**1**		
Warfarin		1		
C01-04 and C07-09: Cardio-vascular drugs	**4**	**12**	**6**	**22**
Loop diuretics		1	2	7
Thiazides		2		
Hydrochlorothiazide + amiloride		1		1
ACE-inhibitors			1	2
Angiotensin II antagonists	1	3		
β-blocking agents	2	2		4
Calcium-blocking agents	1	2	2	4
Long-acting nitroglycerin				4
Digitalis			1	
Comb. candesartan + hydrochlorothiazide		1		
C10: Lipid-reducing agents	**4**	**1**	**1**	**2**
Statins	3	1	1	2
Ezetimib	1			
H01-03, G03: Hormones	**1**	**4**	**5**	**3**
Thyroxin		1	2	2
Glucocorticoid hormones		1	1	1
Oral estrogens		1	1	
Comb. oral estrogens + gestagens			1	
GnRH agonists	1			
Gonadotropin releasing analogue		1		
M01A: Non-steroid anti-inflammatory drugs	**1**			
Ketoprofene	1			
M05B: Bisphosphonates		**2**		
Alendronate		2		
M05B: Combination biphosphonates/calcium			**1**	
N02: Analgetics	**1**	**2**		**4**
Paracetamol	1	1		1
Dextropropoxyphene		1		1
Tramadol				1
Comb. paracetamol + codeine				1

(Continued)

Table 2 - *(Continued)*

	75-79 years	80-84 years	85-89 years	>90 years
N02 and C01: Blood pressure-increasing drugs			1	1
Dihydroergotamine				1
Etilefrin			1	
N05: Psychopharmacological agents	1	4		2
Antidepressive agents		2		1
Major tranquilizers	1			
Hypnotics		2		1
R05: Anti-cough drugs		1		
Cough mixture		1		
S01E: Glaucoma eye drops				3
Timolol				2
Brimonidin				1
Others		2	1	5
Alfuzosin (prostatic gland hyperplasia)				1
Allopurinol (hyperuricemia)				1
Glucosamine (osteoarthritis)			1	1
Na-bicarbonate (acidosis)				1
NaF + apple acid (dry mouth)		1		
Sumatriptane (migraine)				1
Ursodeoxycholic acid (primary biliary cirrhosis)		1		

differences were investigated with the Tukey-Kramer correction for multiple tests. Linear regression was used to study the relationship between various explanatory variables: S-Creatinine, S-Cystatin C, age, gender, body weight, and lean body mass. Explanatory variables were examined one by one and in different combinations to give the model with the best fit. The chosen model was validated using cross-validation (26). To examine model fit graphically, residuals were calculated by taking the difference between GFR predicted by the proposed equation and that measured by Iohexol clearance ($GFR_{Iohexol}$). These residuals were expressed as percentages of $GFR_{Iohexol}$ and plotted against $GFR_{Iohexol}$. Correlation and R^2 values were calculated with Spearman's correlation coefficient. All statistical analyses were performed with SAS 8.2 (SAS Institute Inc. 2005).

RESULTS

A total of 45 subjects completed the study, although only 44 were included in the evaluation and construction of the prediction model, due to one missing S-Cystatin C value. There were no adverse reactions associated with the Iohexol injections. Baseline characteristics are shown in Table 1.

Mean $GFR_{Iohexol}$ for the age group 75-79 years was 70.1 mL/min, for 80-84 years 56.7 mL/min, for 85-89 years 59.1 mL/min, and for >90 years 45.0 mL/min. Only three out of 44 subjects had $GFR_{Iohexol} \leq 30$ mL/min (3/44 <30 mL/min/1.73 m^2 body surface area). The ANOVA showed significant differences in baseline values for pADL, body weight, body mass index, and measured GFR. Pair-wise tests for the various age groups were carried out and significant differences are shown in Table 1. For the other baseline characteristics, there were no statistically significant differences between the four age classes, including lean body mass, various measurements of blood pressure, and number of continuously taken medicinal drugs.

Table 2 lists all continuously taken drugs, grouped according to the World Health Organisation ATC classification (27) in the four age-groups.

In total, the participants had medical drug prescriptions from 19 major pharmacological groups, comprising 64 substance classes. Heterogeneity in medical prescriptions in the four age groups was too large to warrant an ANOVA.

Figure 1 shows a scatter plot in which GFR predicted by the Cockcroft-Gault equation calculated for each in-

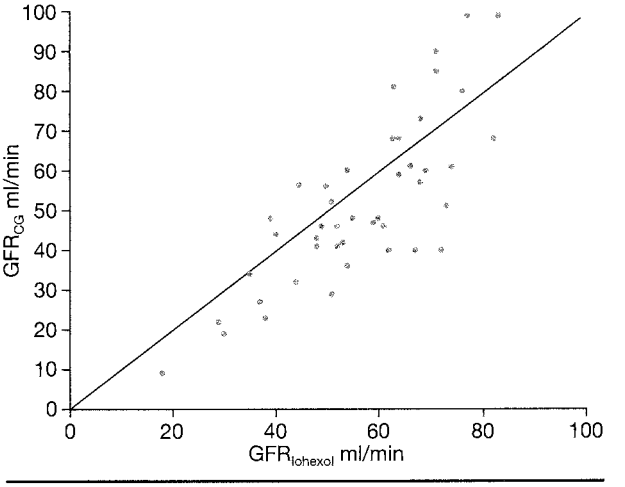

Fig. 1 - Scatter-plot for GFR predicted by Cockcroft-Gault equation (GFR_{CG}) vs GFR measured by Iohexol clearance ($GFR_{Iohexol}$). Line indicates where methods would give same results.

dividual (GFR_{CG}) is plotted against the actual $GFR_{Iohexol}$.

Two participants had identical values, giving a plot with 43 markers. Most data points fell below the identity line, indicating that GFR_{CG} systematically underestimates GFR in this elderly population. The average bias, systematical error, was -5.3 mL/min (SD 12.4).

Prediction equation

The inverse of both S-Creatinine and S-Cystatin C were linearly related to GFR, although the variability of the inverse of S-Cystatin C as explanatory variable was smaller. Of all variables investigated, S-Cystatin C had the greatest predictive value and was therefore used as the primary variable in the equation. The other variables (age, gender, body weight, lean body mass, serum creatinine) were investigated in a multivariate, linear regression model together with the inverse of S-Cystatin C, without improving the model further.

After all variables had been examined, and none selected, quadratic and cubic terms of the inverse of S-Cystatin C (1/(S-Cystatin C)^2 and 1/(S-Cystatin C)^3) were investigated to see if they could improve model fit and yield a larger degree of explanation of the variation in measured $GFR_{Iohexol}$. A cubic term improved the fit marginally, but the improvement was judged not large enough to warrant the addition of another term to the model. The final choice was therefore a linear model with the inverse of S-Cystatin C as explanatory variable and an intercept. GFR estimated by this prediction equation is shown as GFR-Akner (GFR_A) with the following estimated coefficients:

$$GFR_A = 8.3 + 54.5 \cdot \frac{1}{\text{S-Cystatin C}} \quad \text{or, equivalently,} \quad GFR_A = 8.3 + \frac{54.5}{\text{S-Cystatin C}}$$

This prediction equation is not gender-specific: when S-Cystatin C was used instead of S-Creatinine in the prediction equation, there seemed to be no gender-specific differences in estimated GFR. Gender-specific effects were, however, evident when S-Creatinine was used as explanatory variable in a corresponding linear model, with the inverse of S-Creatinine as explanatory variable.

The above equation is based on prediction of total GFR without correction for body surface area (BSA). Expressing GFR by BSA, where BSA was based on bodyweight and height (24), did not improve the predictions further. The number of subjects was, however, small and it was still possible that correction for BSA would improve the fit. This issue needs to be examined in a larger study. The final model gave an R^2 of 0.78 for GFR_A *vs* $GFR_{Iohexol}$ compared with 0.64 for GFR_{CG} *vs* $GFR_{Iohexol}$. This indicates that a model with only the inverse of S-Cystatin C as explanatory variable has greater predictive value compared with the Cockcroft Gault equation, at least in this elderly population.

Evaluation of prediction equation by cross-validation

The described prediction equation was evaluated by a cross-validation method (26), briefly described as follows: all observations in the data set - except the observation from one individual denoted "i" - were used to estimate the coefficients in the prediction above equation. The estimated coefficients were then used to predict GFR for individual "i". This procedure was iterated for each individual in the dataset.

Figure 2 shows estimated GFR_A for each individual calculated by the cross-validation procedure described above, in a scatter plot against $GFR_{Iohexol}$.

The estimates appear unbiased, i.e., approximately equal numbers of data-points appear on each side of the identity line. The variance is also notably smaller (the data-points are closer to the line), when the residuals for GFR_A *vs* $GFR_{Iohexol}$ were compared with the biased scatter plot of GFR_{CG} *vs* $GFR_{Iohexol}$ in Figure 1.

Bias and mean absolute differences

As stated earlier, the mean bias for GFR_{CG} was -5.3 mL/min (SD 12.4), i.e., the Cockcroft-Gault equation gave a mean underestimation of GFR of 5.3 mL/min. The corresponding bias for the GFR_A was only 0.1 mL/min (SD 7.5).

An alternative way of describing variability, i.e., by how much the predictions of GFR deviate from the true GFR, is mean absolute difference. The absolute difference is always positive and is defined as follows (vertical bars indicate 'take positive value of'):

$$\text{mean absolute difference} = |\text{Actual clearance} - \text{Predicted clearance}|$$

The mean absolute difference for the GFR_{CG} prediction

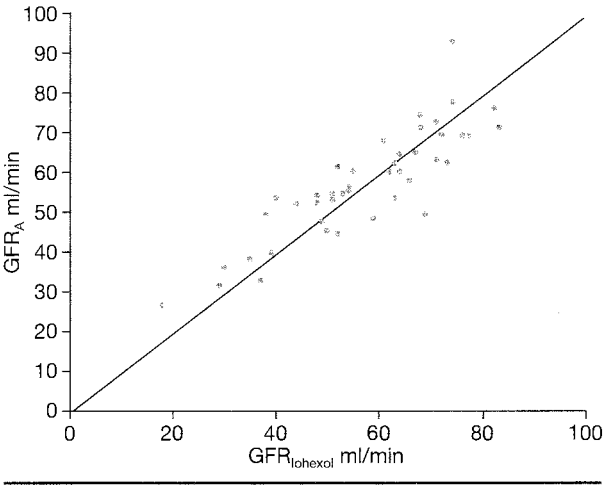

Fig. 2 - Scatter-plot for GFR predicted by equation presented here (GFR_A) vs GFR measured by Iohexol clearance ($GFR_{Iohexol}$). Line indicates where methods would give same result.

was 11.4 mL/min (SD 7.1) and that for the GFR_A prediction was 5.9 mL/min (SD 4.5). When the mean bias of 5.3 mL/min for the GFR_{CG} was subtracted from each predicted clearance, the mean deviation for the corrected GFR_{CG} was still as high as 9.8 mL/min (SD 7.4), i.e., the mean absolute difference for GFR_A compared with true clearance is considerably smaller than for GFR_{CG}.

Still another way of presenting how well the different prediction equations describe actual GFR is first to calculate residuals as differences between predicted and measured GFR. However, a residual of - for example - 10 mL/min should be viewed in the light of the true GFR for that individual. A misprediction of 10 mL/min is much more important when the true filtration rate is 20 mL/min compared with 80 mL/min. Therefore, each residual is expressed as a percentage of measured GFR. The residuals for the GFR_{CG} and GFR_A are shown in Figs. 3-4, respectively.

As noted above, the residual for each individual is calculated by the cross-validation procedure. The residuals for the predictions are randomly distributed, but with a fairly high variance. The variance for the residuals with GFR_A is smaller, and there may be a slight trend with positive residuals for lower measured GFR values. This needs to be examined further in a larger data-set.

DISCUSSION

In geriatric medicine and care for the elderly, there is a great need to predict GFR by means of a prediction equation, both during acute admissions to hospital and on a regular basis in rehabilitation facilities, nursing homes and primary care (28). If the prediction indicates a reduced GFR and the clinical picture or management requires detailed knowledge of renal function, it is sometimes

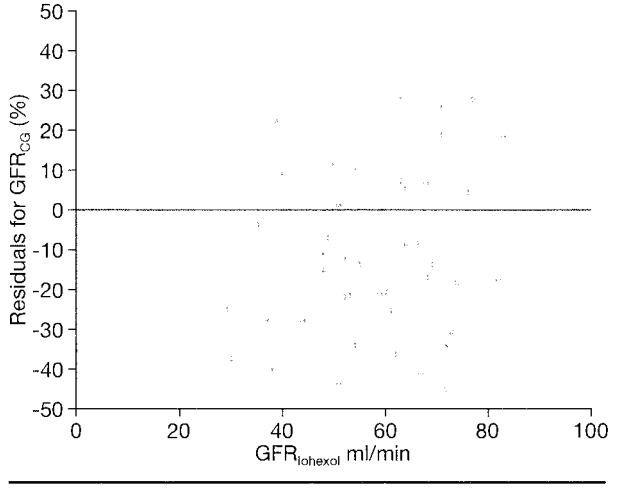

Fig. 3 - *Residuals calculated as GFR_{CG} minus $GFR_{Iohexol}$, expressed as percentage of true GFR ($GFR_{Iohexol}$), plotted against $GFR_{Iohexol}$.*

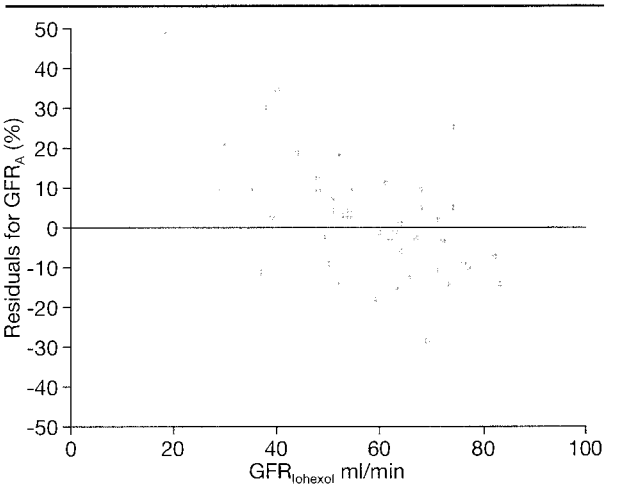

Fig. 4 - *Residuals calculated as GFR_A minus $GFR_{Iohexol}$, expressed as percentage of true GFR ($GFR_{Iohexol}$), plotted against $GFR_{Iohexol}$.*

necessary to proceed with measuring GFR, and the predicted GFR is valuable in estimating the proper blood sampling time necessary for accurate GFR determination.

It has been reported that 20.6% of all non-institutionalized people 65 years and older in the USA has moderately or severely reduced renal function (29). In order to facilitate clinical analysis, as well as to adjust dosing of drugs with renal clearance to optimize treatment effects and minimize the risk of adverse drug reactions, it is therefore vital to monitor renal function regularly in elderly people over time, especially in patients with several morbid conditions and multiple medication prescriptions.

The elderly subjects studied here exhibited clinical multimorbidity, expressed as a large heterogeneity of continuously taken medicinal drug as regards both number and type. As expected, cardio-vascular drugs dominated the prescriptions. Average renal function declined between the age-groups, although again with large individual variations.

A newly developed equation for GFR prediction in elderly people, designated GFR_A, uses the inverse of serum cystatin C as a single explanatory variable together with two estimated coefficients. The equation predicts GFR measured as Iohexol clearance in ambulatory community-dwelling elderly people 75 years and older with an average underestimation of only 0.1 mL/min. The proposed prediction equation was evaluated by cross-validation and provided an unbiased estimate with lower variance compared with GFR_{CG} predictions. The cross-validation procedure was used to give a more unbiased analysis. Residuals were calculated by removing one individual at a time from the data-set; hypothetically, the values of this individual were independent of the other observations used to calculate the coefficients in the equation. However, since all indi-

viduals were drawn from a rather homogeneous population of community-dwelling elderly people, they are to some degree more similar to each other than randomly chosen individuals in a population of elderly inpatients. The results in clear favour of the GFR_A prediction should be viewed in the light of this.

There is accumulating evidence that S-Cystatin C is superior to S-Creatinine in estimating actual GFR (8). A recent meta-analysis of 54 previous studies of all ages and across all values of renal function showed that the overall correlation coefficient for the reciprocal of S-Cystatin C is superior to that of the reciprocal of S-Creatinine when compared with various GFR reference standards (30). In addition, the inverse of S-Cystatin C has been found to be reliable in estimating renal function in a variety of diseases, e.g., cancer (31), diabetes mellitus Type 1 (32) and Type 2 (33), rheumatoid arthritis (34), liver cirrhosis (35) and in renal transplants (36).

Our results with S-Cystatin C to predict GFR in the elderly are in accordance with some previous studies directed at this age-group (37-39) but not with others (40, 41), in both cases according to GFR reference standards. The probable reason for these discrepancies may be differences in methodology (e.g., GFR reference method, length of sampling after injection of exogenous marker, analytical issues, etc.) and study populations (e.g., age, outpatients/inpatients, degree of renal function impairment, drug treatment, etc.).

There are several strengths with the presented prediction equation: i) it is based on community-dwelling elderly (75+) men and women in stable health; ii) it is based only on the endogenous GFR marker, serum cystatin C, and does not include age, gender, body weight or serum creatinine; iii) it is validated against a direct gold standard measurement of 3-point Iohexol clearance. It is well known that the time period for sampling serum-iodine must be gradually prolonged with declining renal function (4) and it is therefore particularly important in geriatric care. To our knowledge, this is the first study using a 3-point Iohexol clearance in an elderly population with one time-point as late as 7 hours. It has been reported that the optimal time for sampling an expected GFR <40 mL/min/1.73 m^2 is 10 hours (42), although this long sampling time was not possible in our patient population in outpatient care, for practical reasons.

One weakness of our study is the relatively small patient sample and the relatively few individuals with substantially impaired renal function - only 3/44 participants had a measured GFR ≤30 mL/min/1.73 m^2. This may be due to selection bias, since participants were recruited from a group of elderly people who had a positive attitude toward participating in clinical research activities and may therefore represent a more healthy sample of those over 75 in the community with well-preserved renal function, in line with previous reports that renal function does not always decline with age (43-46).

There are several potential confounders when S-Cystatin C is used as a marker for renal function. Several non-renal factors that may increase S-Cystatin C have been identified, such as hyperthyroidism (47), presence of rheumatoid factor (48), microalbuminemia/proteinuria, oral treatment with glucocorticoid hormones, and index of reduced physical function (49). Such medical confounders may cause particular problems in estimating GFR in the multimorbid elderly.

A recent study found that serum cystatin C depended on lean body mass in 77 patients with chronic renal disease, mean age 65, and that the GFR prediction equation was significantly improved by combining these two variables (50). These results are in contrast to another study also directly investigating the relationship between serum cystatin C and body composition (51).

In the present study, we used simple anthropometry to calculate lean body mass, whereas the other two studies used dual energy x-ray absorptiometry (DXA). Moreover, our patients were older than in those studies.

One may question if there is a need to construct an equation to predict actual measured GFR, or if it is enough to simply use direct measurement of S-Cystatin C as a marker for GFR. This is an important issue, since mathematical transformations of the S-Cystatin C value introduce intercepts and slopes with uncertain faults. It has been suggested that a normal GFR may be evaluated by simply studying the S-Cystatin C level in mg/L, since this level is virtually the same for persons of both sexes aged between 1-50 years and increases with age, in parallel with GFR decrease (25). However, in geriatric care, many patients have reduced renal function and we believe that clinicians need a physiological estimate of the actual GFR in order to be able to manage information on renal function. This subject warrants our report of a new GFR prediction equation specifically designed for elderly people 75 years and older.

CONCLUSIONS

To our knowledge, this is the first study in which GFR has been measured by the 3-point Iohexol clearance method in randomly selected community-dwelling elderly people, 75 years and over.

We propose a prediction equation, GFR_A, based on the inversion of S-Cystatin C, which is independent of gender, body surface area, body weight, lean body mass and S-Creatinine. It is clearly more precise than GFR_{CG}, although it needs to be validated in a larger population of elderly subjects, including more individuals in stable health with substantially reduced renal function in whom GFR is measured by a reference method with adequate sampling time.

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