Cardiovascular risk factors in patients with chronic kidney disease: The Chronic Renal Impairment in Birmingham (CRIB) Study.

David Wheeler, John Townend, Martin Landray.

The evolution of cardiovascular diseases among patients with chronic kidney disease (CKD) not requiring dialysis has not been well studied. The CRIB cohort comprises 369 individuals with CKD not receiving renal replacement therapy at baseline assessment, which took place between December 1997 and September 1999. Two age- and sex-matched control groups, one comprising 103 patients with angiographically-proven coronary artery disease and the other 103 apparently healthy individuals were also studied at baseline. Of the patients with kidney disease, 34% had vascular disease and 21% left ventricular hypertrophy according to electrocardiographic criteria. Traditional risk factors included a history of hypertension in 76%, diabetes in 15% and dyslipidaemia with reduced low-density lipoprotein cholesterol, elevated triglyceride and decreased high density lipoprotein cholesterol levels. Other possible risk factors included elevated levels of plasma homocysteine, a low serum albumin, an elevated C-reactive protein and a low haematocrit. In a subgroup of 270 CKD patients, we noted reduced levels of 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 compared to controls, with concomitant elevations in parathyroid hormone, even in patients in the upper tertile of kidney function based on plasma cystatin C (equivalent to mean estimated creatinine clearance of 40 ml/min). Four year follow-up of this cohort has just been completed allowing assessment of cardiovascular and renal outcomes in relation to baseline risk factors. Results to date suggest that cardiac and vascular diseases are prevalent in CKD patients not requiring dialysis and that both traditional and non-traditional risk factors may contribute.

Independent Components of Chronic Kidney Disease as a Cardiovascular Risk Factor: Results from the Kidney Early Evaluation Program (KEEP)

Peter A. McCullough, MD, MPH, Wendy Brown, MD, Janet McGill, MD, Alan Collins, MD, Shu-Cheng Chen, MS, Suying Li, MS, Ajay Singh, MD, Andrew Narva, MD, William H. Herman, MD, MPH, George L. Bakris, MD, Claudine Jurkovitz, MD, Keith Norris, MD, Pablo Pergola, MD, Michael Klag, MD.

Background. Chronic kidney disease (CKD) is recognized as an independent cardiovascular disease (CVD) risk state and has been defined by levels of estimated glomerular filtration rate (GFR) and the presence of microalbuminuria. Anemia is a common comorbidity in CKD. The relative independent relationship between these three CKD-related measures, and CVD is not fully known.
Methods. The Kidney Early Evaluation Program is a multicenter screening program of individuals at risk for CKD. Estimated GFR was computed using the 4-variable MDRD equation based on serum creatinine, age, gender, and race. Of 24,070 (age 52.6±15.8 years, 68.9% female, 39.4% African American) who volunteered for screening, 3,883 (16.1%) had a self-reported history of CVD (myocardial infarction, stroke, peripheral artery disease). Multivariate analysis found that age > 75 years (referent: 46-60), OR=2.17, 95% CI 1.89-2.50, p<0.0001; male gender, OR=1.20, 95% CI 1.09-1.33, p=0.0004; urine microalbumin > 30 mg/L (referent: $\leq$ 10); OR=1.63, 95% CI 1.46-1.82, p<0.0001; GFR 30-59 ml/min (referent: $\geq$ 90), OR=1.37, 95% CI 1.20-1.57, p<0.0001; GFR<30 ml/min (referent: $\geq$ 90), OR=1.84, 95% CI 1.31-2.59; p=0.0004; and hemoglobin < 12.8 g/dl (referent: >14.6), OR=1.45, 95% CI 1.27-1.66, p<0.0001, were all independently associated with CVD. Conversely, African American race was inversely related to self-reported CVD (referent: white), OR=0.83, 95% CI 0.75-0.92, p=0.0003. Those with all three CKD-related factors had a 35.8% prevalence of CVD.
Conclusions: Among individuals who volunteered for this screening program, CVD was common. Estimated GFR, microalbuminuria, and anemia contribute to the reported cardiovascular risk in CKD patients, and when all three are present, over one-third of individuals had known CVD.

Changes in urine albumine and in serum creatinine in people at high CV risk: data from the HOPE study

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In people with diabetes, renal disease tends to progress from microalbuminuria to clinical proteinuria to renal insufficiency. Little evidence has been published for the non-diabetic population. We retrospectively analyzed changes of proteinuria over 4.5 years in the HOPE (Heart Outcomes and Prevention Evaluation) study which compared ramipril's effects to placebo in 9,297 participants, including 3,577 with diabetes, and 1,956 with microalbuminuria. nclusion criteria were known vascular disease or diabetes plus one other cardiovascular risk factor, exclusion criteria included heart failure or known impaired left ventricular function, dipstick-positive proteinuria (>1+) and serum-creatinine >2.3 mg/dl (200 uM). Baseline microalbuminuria predicted subsequent clinical proteinuria for the study participants overall (adjusted odds ratio, OR 17.5 ; 95% confidence interval, CI 12.6 – 24.4), in participants without diabetes (OR 16.7; 95% CI 8.6 – 32.4) and in participants with diabetes (OR 18.2; 95% CI 12.4 – 26.7). Any progression of albuminuria (defined as new microalbuminuria or new clinical proteinuria) occurred in 1,859 participants: 1,542 developed new microalbuminuria and 317 participants developed clinical proteinuria. Ramipril reduced the risk for any progression (OR 0.87; 95% CI 0.78 – 0.97, p= 0.0146). People without and with diabetes who are at high risk for cardiovascular disease, are also at risk for a progressive rise in albuminuria. Micro-albuminuria itself predicts clinical proteinuria in non-diabetic and in diabetic people. Ramipril prevents or delays the progression of albuminuria.

We also analyzed yearly changes of serum-creatinine in the 3,577 participants with diabetes, including 1,139 with microalbuminuria, and 333 with renal insufficiency. Follow-up serum-creatinine was not available in non-diabetics. Serum-creatinine did not significantly increase during the study if all diabetic participants are considered or in subgroups with microalbuminuria and/or with renal insufficiency at baseline. However, slopes of serum-creatinine over time showed a significant trend for increasing values. There were no differences between with placebo- and ramipril treated groups. A serum-creatinine $\geq$ 1.4 mg/dl newly developed in 474 / 3,238 people (243 on placebo and 231 on ramipril, p =0.5033). A doubling of baseline serum-creatinine or end stage renal disease developed in 8 of those 333 participants with renal insufficiency at baseline. In people with type 2 diabetes but without overt nephropathy who are at high risk for cardiovascular disease, progression of renal insufficiency is slow on the basis of changes of creatinine. On the basis of reaching threshold levels of renal function, progression rates are clinically meaningful, especially considering population life expectancy.

Age Over 30 Becomes a Cardiovascular Risk Factor in Patients Screened for Chronic Kidney Disease: Results from the Kidney Early Evaluation Program (KEEP)

Peter A. McCullough, MD, MPH, Michael Klag, MD, Janet McGill, MD, Alan Collins, MD, Shu-Cheng Chen, MS, Suying Li, MS, Ajay Singh, MD, Andrew Narva, MD, William H. Herman, MD, MPH, George L. Bakris, MD, Claudine Jurkovitz, MD, Keith Norris, MD, Pablo Pergola, MD, Wendy Brown, MD.

Background. Chronic kidney disease (CKD) is recognized as an independent cardiovascular disease (CVD) risk state and has been defined by levels of estimated glomerular filtration rate (GFR) and the presence of microalbuminuria. There is an age-related decline in renal function down to an estimated GFR of 60 ml/min during normative aging. Among patients with CKD, the influence of age on the risk of CVD is unknown.

Methods. The Kidney Early Evaluation Program is a multicenter screening program of individuals at risk for CKD but not on dialysis. Estimated GFR was computed using the 4-variable MDRD equation based on serum creatinine, age, gender, and race. Of 24,070 (age 52.6±15.8 years, 68.9% female, 39.4% African American) who volunteered for screening, 3,883 (16.1%) had a self-reported history of CVD (myocardial infarction, stroke, peripheral artery disease). Multivariate analysis set age 18-30 as the referent. With each increasing age group there was a linear increase in the risk of CVD after age 30 (Table). Other significant factors in the model were male gender, OR=1.27; hypertension, OR=1.64; diabetes, OR=1.73; smoking, OR=1.56; microalbuminuria >30 (reference: ≤10), OR=1.34; anemia (Hb ≤12.8) (referent: >14.6 g/dl), OR=1.42; and body mass index > 30 (referent: <25 kg/m^2), OR=1.33 (all p<0.0001).

Conclusions: Among individuals who volunteered for kidney disease screening, age acts as a CVD risk factor starting at age 31, and having the strongest association with CVD of any conventional cardiac or renal risk factor. These data suggest CKD amplifies the age effect on atherosclerosis and potentially accelerates its course in young individuals.

Table. Independent odds ratio (OR) for CVD according to age group.

	OR	Lower	Upper	P
Participant Age				
18-30	reference			
31-45	1.444	1.102	1.891	0.0077
46-60	2.396	1.844	3.113	<.0001
61-75	4.019	3.07	5.262	<.0001
>75	6.398	4.793	8.54	<.0001

MODIFICATION OF THE NATIONAL KIDNEY FOUNDATION CLASSIFICATION OF CHRONIC KIDNEY DISEASE (PUERTO RICO CLASSIFICATION)

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As the incidence of the end-stage renal disease (ESRD) increases in the general population, so does the need for early identification of patients with chronic kidney disease (CKD) with the goal in mind of applying treatment strategies that will slow its progression. The National Kidney Foundation (NKF) Clinical Practice Guidelines for CKD Evaluation, Classification, and Stratification, published in February 2002, provides a method of classification, disregarding of the etiology of the kidney disease with the purpose of helping define the epidemiology of CKD and its complications. It also provides a scheme for the management of patients with CKD, recommending a clinical action plan for each stage. The Puerto Rico classification of CKD uses the NKF categories and integrates subclassifications for the degree of hypertension (JNC VI) and albuminuria that a patient exhibits,as these are important indicators in CKD progression . The JNC (VI) was selected for the following reasons: (1) it stratified categories of blood pressure,better depicting a graded relationship of each category in the prediction of end stage renal disease;(2) each 10 mm Hg increase in systolic blood pressure also forecast progression of ESRD. It has been suggested that addressing these factors, might slow the progression of CKD, but if caught early enough, may halt it altogether.

Conclusion: The proposed modification enables more accurate patient monitoring and an objective evaluation of preset targets, which is accomplished by utilizing a matrix and follow-up chart which can be used to model a priori the individual risk of progression to ESRD.

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TABLE 1. MATRIX OF CLASSIFICATION, REMISSION AND REGRESSION OF CHRONIC KIDNEY DISEASE FOLLOW-UP AND EVALUATION CHART

FOLLOW UP CHART

VARIABLES		CLASSIFICATION	TIME (expressed in months)								MATRIX
			INITIAL								
GFR (cc/min)		Stage									
	> 90	I									
	89-60	II									
	59-30	III									
	29-15	IV									
	< 15	V									
BLOOD PRESSURE (mmHg)		Grade									
	< 120/80	A									
	< 130/85	B									
	130-139/ 85-89	C									
	140-159/ 90-99	D									
	160-179/ 100-109	E									
	≥ 180/110	F									
ALBUMIN (mg/24hs)	(in urine) < 30	Level									
		1									
	30-300	2									
	> 300	3									
RISK FACTORS	(in blood) Glucose and Hb A_1c										
	Cholesterol and LDL										
	Ca, P , PTH										
	Hb										
PRESCRIPTIONS											

MODIFICATION OF THE NKF CLASSIFICATION OF CKD

Puerto Rico Classification

STAGES	BLOOD PRESSURE, mm Hg		Albuminuria
	Systolic	Diastolic	
Stage I GFR=≥ 90cc/min Kidney Damage with normal or increased GFR.	A. < 120	< 80	Level I < 30mg/24h
Stage II GFR= 60-89 cc/min MILD decreased in GFR	B. < 130	< 85	
Stage III GFR= 59-30cc/min Moderate Decrease in GFR	C. 130-139	85-89	Level II 30-300 mg/24h
Stage IV GFR= 29-15cc/min Severe Decrease in GFR	D. 140-159	90-99	Level III > 300 mg/24h
	E. 160-179	100-109	
Stage V GFR= 15cc/min Kidney failure or dialysis	F. ≥ 180	≥ 110	

Dr. Rafael Burgos Calderón
San Juan, PR.
Sept./2004

AGENDA FOR THE FUTURE

Integrated Approach*

Cardiovascular ⇄ Kidney ⇄ Endocrine-Metabolic

MODIFICATION OF THE NKF CLASSIFICATION OF CKD

Puerto Rico Classification

STAGES	BLOOD PRESSURE, mm Hg		Albuminuria
	Systolic	Diastolic	
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Stage V GFR= 15cc/min Kidney failure or dialysis	F. ≥ 180	≥ 110	

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*CAREM/RENAL HEALTH

Abstract
Joris R. Delanghe

Urinalysis, specific proteins and creatinine standardization are among the research interests of Dr J Delanghe (Dept of clinical chemistry, University Hospital Gent, Belgium). At present, the issue of creatinine restandardisation is one of his research topics. In the sixties and seventies, the advent of laboratory automation induced a protein error in creatinine determination. By the year 1980, the classical text books did no longer corresponded with the clinical reality of creatinine measurement. At present, this practice is no longer generally accepted. Recent European Union In vitro diagnostics (IVD) regulations have initiated restandardisations for creatinine by a number of vendors. Unfortunately, the IVD industry did not apply a uniform standardisation for creatinine. In consequence, a broad inter-laboratory variation still is present. A major concern in this respect is the use of derived formulas for calculation of creatinine clearance (Cockroft and Gault, MDRD in adults, Schwartz in children). Especially in the younger age groups (1-3 years), the variations between creatinine methods are still very pronounced. “Uncompensated” Jaffe methods are not compatible with Cockroft and Gault formula, whereas the enzymatic and so-called “compensated” Jaffe methods are not compatible with Schwartz formula. The present lack of creatinine standardisation has major consequences for the clinician and the pharmacologist, who often are unaware of the situation (references: Clin Chem 2003; 49: 163;49:1011-1014; Accreditation and Quality control 2005; in press).

LOOKING FOR A FEASIBLE MARKER OF GLOMERULAR FILTRATION RATE: AN ARGENTINEAN PERSPECTIVE

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Background. Glomerular filtration rate (GFR) is often estimated from plasma creatinine, however it has long been recognised that exceeds true GFR. Cimetidine improve the accuracy of GFR due to inhibition of tubular creatinine secretion. We designed a study to compare the performance of GFR prediction from traditional equations and serum markers including cystatin C with GFR measurement by cimetidine modified creatinine clearance (CMCC) as reference method.
Methods. The endogenous creatinine clearance was measured in 41 outpatients in a 2-hr urine collections before and after (CMCC) a single intravenous bolus of cimetidine. GFR estimation was calculated with reciprocal of serum creatinine and cystatin C, Cockcroft-Gault, abbreviated MDRD, Walser and Jelliffe 2 equations. Their overall relationship and performances were compared with CMCC.
Results. Each GFR prediction model displayed a highly significant correlation ($p< 0.001$). Correlation coefficients (r) varied from 0.730 for reciprocal of creatinine to 0.864 for reciprocal of cystatin C. The better and worse mean predicted GFR respectivelly ranged from 60.5 ml/min/1.73 m^2 for Jelliffe 2 to 81.6 ml/min/1.73 m^2 for reciprocal of serum creatinine (CMCC:52.09 ml/min/1.73 m^2); the median absolute difference from 7.35 ml/min/1.73 m^2 to 26.1 ml/min/1.73 m^2 and the mean percent error in prediction from 12.5 % to 36.1 %. Jelliffe 2 and Walser equations gave the lowest bias (8.46 ml/min/1.73m^2) and the highest precision (14.66 ml/min/1.73 m^2) respectively, however no more than 58,8% of estimated values were within ± 20% error.
Conclusions. Predicted GFR values by the equations tested and reciprocal of serum markers correlated well with the measured GFR. Jelliffe 2 and Walser equations gave the best performances, however all equations showed a tendency towards GFR overestimation. This study help to define the most performing methods for estimate renal function in Argentina.

Estimating renal function; common causes of confusion and error.

James Tattersall, Leeds, UK

K-DOQI guidelines recommend staging of kidney disease according to the estimated surface-area normalised GFR by the MDRD method.
Other methods for estimating renal function in common use return results which may not be comparable to the MDRD GFR. This causes confusion and significant miss-classification of the stage of renal disease.

Creatinine clearance from 24h urine collections.
Due to tubular creatinine secretion, creatinine clearance is always higher than GFR. The difference is particularly great when GFR is low so that creatinine clearance is approximately twice the GFR when GFR is 15 ml/min.
Creatinine clearance should be normalised to a surface area of 1.73 m^2 by multiplying by 1.73 and dividing by surface area estimated from height and weight. There are three different methods for estimating surface area (all of which are recommended by DOQI). Laboratories almost invariably calculate creatinine clearance from 24hr urine collections without any surface-area normalisation.

Cockcroft and Gault method.
Recommended by the Australian CARI guidelines and others. It returns Creatinine clearance which is not normalised to surface area. The estimation includes input of weight to 'de-normalise' the result for surface area so that it is comparable to the result of measurement from 24hr urine collections uncorrected for surface area. The combination of the effects of the 'de-normalisation' and tubular creatinine secretion may cause the creatinine clearance by the Cockcroft and Gault method to be up to four times greater than GFR by the MDRD method in small patients with low GFR.

Different methods for measuring serum creatinine concentration
Most laboratories use the Jaffe method which is non-specific and overestimates serum creatinine by a mean of 0.23 mg/dl (20 mmol/l). This causes the MDRD method to underestimate GFR. This error is relatively greater at normal GFR, the elderly and in females when the creatinine level is low. The GFR calculated by the MDRD method may underestimate GFR by up to 40 ml/minute in elderly females with near-normal GFR. This will result in a false-positive if the MDRD method is used for screening.

Without clearer standardisation in the methodology for quantifying renal function, there is significant potential for confusion and error in interpreting data and application of guidelines.
Patients with severe renal failure (stage 5) could be miss-classified as stage 3. This miss-classification is relatively more likely in small elderly females.

Detection of Chronic Kidney Disease in a Commercial Clinical Laboratory

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Abstract

Background and Methods: Chronic kidney disease is a major public health problem, with increasing incidence and prevalence, poor outcomes and high costs. Improving outcomes requires early identification; laboratory test results and diagnostic codes can be utilized for this purpose. To determine frequency of testing for serum creatinine, prevalence of estimated glomerular filtration rate <60 ml/min/1.73m^2, and sensitivity of diagnostic codes for kidney disease compared to laboratory test results, we undertook a cross-sectional analysis in regional laboratory of Laboratory Corporation of America located in Columbus, Ohio. Patients with $\geq$40 years with one or more laboratory tests between April 1 2002 and March 31, 2003 were included. Risk factors for chronic kidney disease were defined as age >60 years, diabetes or hypertension.

Results: Of the 277,111 patients who had a laboratory test, 19% had a measurement of serum creatinine, compared to 33% and 71% who had measurements of serum glucose and lipids, respectively. Patients with risk factors for chronic kidney disease were more likely to be tested for serum creatinine. Among patients who were tested, 30% had an estimated GFR <60 mL/min/1.73 m^2. Among patients with estimated GFR <60 ml/min/1.73 m^2, 70% of men and 89% of women had serum creatinine within the normal range. Sensitivity and specificity of kidney disease diagnostic codes compared to estimated GFR <60 mL/min/1.73m^2 were 11% and 96%, respectively.

Conclusions: Identification of patients with CKD from electronic databases will be limited due to low rates of testing for serum creatinine, discrepancy between GFR <60 mL/min/1.73 m^2 and elevated serum creatinine, and low sensitivity of diagnostic codes.

SERUM CREATININE AS MARKER OF RENAL FUNCTION IN SOUTH ASIANS: A STUDY OF REDUCED GFR IN ADULTS IN PAKISTAN

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ABSTRACT:

Background

Migrant populations of South Asian origin have a higher risk of chronic kidney disease (CKD) than the native Caucasians. However, prevalence of CKD has not been studied in South Asia. Several formulas have been developed to estimate kidney function from serum creatinine concentration. However, none of these have been validated in the South Asian population.

Methods

A population based cross sectional study was performed on 292 subjects aged $\geq$ 40 years in Karachi, Pakistan. Reduced GFR was defined as creatinine clearance (Ccr) measured in 24 hour urine collection of less than 60 mL/min/1.73 m^2. Sensitivity and specificity of serum creatinine was calculated by receiver operating characteristic (ROC) curves for reduced GFR. The correlation and agreement among Cockcoft Gault (CG) and MDRD GFR estimation equations with measured Ccr were assessed using regression analysis and Bland Altman method, respectively.

Results

The overall prevalence (95% CI) of reduced GFR was 29.9% (24.2-35.1%): 26.7% (20.1-34.6%) in men and 32.5% (24.8-41.3 %) in women. A cutoff value of serum creatinine of 0.91 mg/dl and 0.73 mg/dl yielded sensitivity of 74% and 82%, and specificity of 68% and 73% specificity in men and women, respectively, for the presence of reduced GFR.

The regression coefficient (r) (95% CI) was superior for MDRD GFR (0.90, 0.80-1.00) CG GFR (0.82, 0.75-0.89), and difference between the two was significant (p=0.003). However, 95% of individual predicted values of MDRD GFR and CG GFR equations were between 65.2 and 64.4 cc/min/1.73 m^2 of measured Ccr, respectively. The proportion of estimates within 20%, 30% and 50% of measured Ccr values were 40.1 vs 47.7% (p=0.18), 58.8 vs 64.9% (p=0.19), and 78.6 vs 79.4% (p=0.85) for MDRD vs CG GFR, respectively.

Conclusions

The high prevalence of reduced GFR in Pakistan deserves immediate attention for institution of effective detection and prevention strategies. Lower levels of serum creatinine in South Asians than those reported for Caucasians mark presence of reduced GFR. In South Asians, the MDRD and CG GFR prediction equations have good correlation but poor agreement with measured Ccr. Studies are needed to develop and validate GFR prediction equations for standardized method for measuring GFR in this population.

How accurate is the estimated GFR by Cockcroft-Gault formula and MDRD equation in Japanese patients?

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When we discuss the international standard equation for estimating GFR from serum creatinine, the following three points should be taken into accounts; 1) the accuracy of the equation should be verified by measured GFR. Cockcroft-Gault formula was originally proposed to estimate creatinine clearance (Ccr). The equation developed from MDRD study (MDRD equation) was proposed as a method to estimate GFR. 2) The fact that serum creatinine depends on not only GFR but also the muscle volume cast doubts to apply a single standardized equation for all ethnic groups, whose physical constitution varies considerably. 3) The results of serum creatinine measured with Jaffe's method (alkaline picrate assay) are higher than those measured with enzymatic method. Though both methods are used worldwide, Cockcroft-Gault formula and MDRD equation were developed by using the serum creatinine data measured with Jaffe's method.

To test the adequacy to apply Cockcroft-Gault formula and MDRD equation for Japanese people, we performed inulin clearance (Cin) and Ccr simultaneously in 126 Japanese patients with chronic kidney diseases. We measured serum creatinine with both Jaffe's method and enzymatic method, and estimated GFR using Cockcroft-Gault formula and MDRD equation. The average GFR was 35.0(13.0-79.2) ml/min/1.73m^2. Ccr(measured by enzymatic method)/Cin was 1.82 and Ccr(measured by Jaffe's method)/Cin was 1.58, indicating Ccr was much greater than Cin The estimated GFRs by Cockcroft-Gault formula using serum creatinine measured with enzymatic method and Jaffe's method were 1.31±0.40 and 1.14±0.34 and those by MDRD equation were 1.48±0.43 and 1.29±0.35, respectively. Our data suggest that the estimated GFR based on enzymatic method is 16% higher than that based on Jaffe's method, and the estimated GFR by MDRD equation is 13% higher than that by Cockcroft-Gault formula, suggesting that we need more accurate methods for Japanese to estimate GFR from serum creatinine measured with enzymatic method, which is used in 86% clinical laboratory in Japan.

Prevalence of Chronic Kidney Disease in Chile

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For the first time in Chile, 2003, a National Health Survey was conducted in a representative sample of the Chilean population 17 years old and above by age, sex, regions, urban/rural and socioeconomic level (www.minsal.cl). Prevalence rates were estimated from data collected for 21 conditions: major cardiovascular risk factors such as diabetes, dislipidemia, hypertension, obesity, smoking, physical inactivity and for chronic kidney disease, amongst others. Proteinuria was measured in a random urine sample with a dipstick test for albuminuria; glomerular filtration rate (GFR) was estimated from serum creatinine levels by using the Cockcroft equation**.**

Results: Prevalence of major CV risk factors is presented in Table 1. Prevalence of proteinuria was 14, 2% (15.2% in those 17-24 years of age and 22.7% in ages ≥65 years). Prevalence of Stages of Chronic Kidney Disease by GFR is presented in Table 2. Persons with hypertension and diabetes had a significant higher prevalence of decreased GFR.

Conclusions: A task force with members of the Chilean Society of Nephrology and the Ministry of Health will set up guidelines for primary care physicians to increase detection and control of early chronic kidney disease, particularly in a high risk population with CV risk factors.

Table 1
Prevalence of Major CV Risk Factors, NHS, Chile 2003

Condition	Prevalence (%)
Diabetes (≥126 mg/dl en 2 amples)	4.2
Total cholesterol (> 200 mg/dl)	35.4
HDL cholesterol (<40 mg/dl)	39.3
Hypertension (2 measurements in 1 occasion)	33.7
Overweight (BMI 25-29)	37.8
Obesity (BMI ≥30)	23.2
Physical inactivity (<3times/week)	90.8
Smoking (1 or more cigarettes)	42.0

Table 2
Prevalence of Chronic Kidney Disease by Stages, NHS, Chile 2003

Stages of Chronic Kidney Disease	GFR (ml/min x 1.73 m2)	Prevalence (%)
1. Normal or increased GFR	(≥90)	65.6
2. Mild decrease GFR	(60-89)	28.5
3 Moderate decrease GFR	(30-60)	5.7
4. Severely decreased GFR	(15-29)	0.2

PROTEINURIA STRATEGIES IN THE EUROPEAN URINALYSIS GUIDELINES

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The **European Urinalysis Guidelines** (EUG) were given under auspices of the European Confederation of Laboratory Medicine (ECLM) by more than 70 professionals in clinical chemistry, microbiology, and clinical disciplines. Strategies to detect renal disease or urinary tract infections in various patient populations should be based on cost/benefit analyses.

Both minimum and optimum procedures will be applied at different economical situations. The following strategies were recommended for *urine tests*:
General patient populations: unselected individuals: no random testing; patients with unclear symptoms: urine screening for leukocytes, bacteria, erythrocytes (or haemoglobin), albumin (or total protein), and a reference quantity (e.g., creatinine).
Specific patient populations (high-risk individuals for renal disease):
(1) **Minimum** (low economy level): urine albumin (sensitivity 20-30 mg/L) and total protein (sensitivity 50 mg/L), urine particles (presence of haematuria, pyuria, and renal elements);
(2) **Optimum** (more expensive level): Urine albumin (sensitivity 2-10 mg/L), $alpha_1$-microglobulin (sensitivity 2-10 mg/L), or retinol-binding protein, and urine creatinine (or another reference quantity).

Measurements of glomerular filtration rate were not discussed in detail in the EUG. Scandinavian medical communities are generally implementing measurements of serum cystatin C to detect incipient reduction of glomerular filtration rate at least in specific patient groups.

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Renal Health Program for Social Security in Argentina.

A public health sustainable and sustained structure
(Abstract)

Santos Depine, MD, MPH [1], Rafael Burgos Calderón, MD [2], Silvia Agati, MD [3], Mercedes Maronna [4]

Both Latinamerican and Caribbean nations experience great inequities in health care access.

In Argentina, the prevalence of patients in dialysis reaches an average of 530 patients per million inhabitants (PPM), with figures amounting to 999 PPM for Buenos Aires and 333 PPM for the Northeastern area of the country.

At the same time, we can find a great number of asymptomatic patients with albuminuria or modification of glomerular filtration who will become insufficient renal patients and will be likely to develop cardiovascular diseases without proper treatment.

Many renal health detection efforts in the adult population or in vulnerable groups that were attempted without a Systematized Program with Reference and Countereferences have not generated better access to First Level Attention and have also failed to involve Nations in the initiative.

This Renal Health Program in Argentina prompts a paradigm shift from disease to health and intends to systematically take action in the health process – disease – renal care. Planned and scheduled within a Logical Framework, it uses the NKF and Puerto Rico Classification and expands in the First Level of Attention. A cardiovascular, renal and endocrino-metabolic approach helps understand the permanent renal condition as a unifying factor of the vascular endothelial injury.

The Renal Health Program identifies the real demand and does not subsidize service offerings. The information gathered will provide actuarial analysis that will anticipate budget needs and help technological and industrial development, generating jobs and resources and at the same time strengthening the country's GDP.

It will be directly managed from the Special Programs Administration Office (Ministry of Health), agency responsible for the Nation's Reinsurance Fund. The program foresees strong economic incentives for primary stakeholders who can ensure compliance.

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Comparison of GFR Estimating Equations using Serum Cystatin and Creatinine in the MDRD Study Population: Preliminary Data

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Background: It is unknown whether estimating equations including serum cystatin C (Scys) will allow for estimating GFR more accurately than equations based on serum creatinine (Scr).

Design: Cross sectional analysis GFR, Scr and Scyc concentration and demographics and clinical characteristics in patients with chronic kidney disease.

Patients: 1078 patients enrolled in the baseline period of the MDRD Study who had stored serum at the second baseline visit, of whom 698 were randomly selected as the training sample.

Methods: Estimating equations for log GFR using log SCr, log Scys or both with and without age, sex and race were developed by regression analyses. GFR was measured as urinary clearance of ^{125}I-iothalamate. Creatinine was measured using the modified kinetic rate Jaffe reaction (Beckman Synchron CX3). Scys was measured using the Dade Berhring method, an automated particle-enhanced nephelometric assay (PENIA).

Results: Mean GFR, Scr and Scys were 33 ml/min/1.73m^2, 2.3 mg/dl and 2.5 mg/dl. Scr and Scys had an R^2 of 0.86. Table 1 compares the precision and accuracy of the different equations. For all equations, the magnitude of the errors of the estimates of GFR were larger at higher kidney function

Conclusions: Equations that use demographic variables in combination with Scr have higher precision and more accurate than equations with Scys. The use of both Scr and Scys in addition to age, sex and race improves GFR prediction.

Table 1: Comparison of mean precision and accuracy of potential GFR estimating equations

	Precision		Accuracy		
	R2	SD of Δ	|Δ|	% |Δ|	% within 30% of measured GFR
Unadjusted					
1. Scys	79.3	7.3	4.0	14.3	84.2
2. Scr	76.7	8.0	4.8	16.5	81.5
Adjusted*					
3. Scys	80.7	7.1	3.8	13.5	85.5
4. Scr	86.3	6.1	3.2	10.8	91.3
5. Scys + Scr	89.1	5.5	2.8	9.4	93.8

* Adjusted for age, sex and race (African American vs. not African American).

Urine Protein as a Diagnostic Test: (Caring for Australians with Renal Impairment) - CARI Guidelines 2004

Rowan G. Walker on behalf of the CARI Urine Protein as Diagnostic Test Working Group (WG) [1]

CARI Guidelines are evidence-based clinical practice guidelines. Recently published in *Nephrology* [2] was *'Urine Protein as a Diagnostic Test'*. For ***Guidelines Recommendations***, the Level of Evidence required is meta-analysis (Level 1) or at least one properly randomised controlled trial (Level 2). In 4 sets of Guidelines no recommendations were possible using these strict criteria but summary ***Suggestions for Clinical Care*** (based on Level 3 (Comparative studies) or Level 4 (Case series)) are as follows

1. **Testing for Proteinuria**
    a. High Risk Populations – Initial Test ***urine PCR*** (Protein/Creatinine Ratio)
    b. Diabetes and Aboriginal Australians– Initial Test ***urine ACR*** (Albumen/Creatinine Ratio)
2. **Performance characteristics of tests used in the initial evaluation of patients at risk of renal disease.**
    a. Dipstick protein has poor sensitivity and specificity. Dipstick albumen is more reliable but operator dependant
    b. First morning specimen preferred. Random ACR is acceptable
    c. PCR is accurate for protein > 1g/day – timed urine is required for baseline
3. **Evaluation of proteinuria in children ****
4. **Monitoring proteinuria in patients with suspected or known renal disease.**
    a. Timed urine collections are recommended when knowledge of absolute values of proteinuria is required.

The WG noted a number of possible future research directions:

- measures of agreement between and the variability of; morning, random and 24h urine sampling
- the utility of gender specific reference ranges for ACR and PCR in predicting progressive CKD
- the relative benefits/harms of routine screening, the comparative usefulness of proteinuria versus albuminuria as a screening tool and the frequency of testing.

1. CARI Urine Protein as Diagnostic Test Working Group: Nicole Isbel, Fred DeLooze, Martin Gallagher, Paul Glasziou, Cassandra Stone, Steven McTaggert, Stuart McLeod
2. Isbel N, et al; Urine Protein as Diagnostic Test: .*Nephrology* **9** (S3), S3-S22

** Suggestions for Clinical Care for Children not included as not the subject of KD:IGO Meeting

Protein and albumin assays in urine

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Methods for determination of urinary total protein do not fulfil the analytical and medical requirements of quantitative tests. A comparison of different methods revealed, that different forms of proteinuria [prerenal, renal (glomerular, tubular), postrenal] deliver variant results depending on the used method. The reason is, that each single protein (albumin, IgG, α_1-microglobulin, hemoglobin, free light chain etc.) makes a different contribution to the total protein concentration. Additionally the calibrator for the total protein needs to be discussed. In use are diluted serum protein standards or an international accepted albumin standard (CRM 470).
As an alternative procedure the standardized albumin method is suggested for screening, but not all types of proteinuria (tubular proteinuria, Bence Jones proteinuria) are detected.
Though the combination of total protein and albumin measurement seems at the moment to be the best method to minimize the problems and should be discussed.

Monitoring kidney function in type 2 diabetic patients with incipient and overt diabetic nephropathy

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Our aim was to evaluate the agreement between GFR and rate of decline in GFR estimated from the MDRD equation (based on s-Cr, age, gender and race) or estimated from the Cockroft-Gault formula (CG) and measured by the plasma clearance of ^{51}Cr-EDTA. A cohort of type 2 diabetic patients with microalbuminuria n=156, 117males, mean (SD) age 55 (7), BMI 29.8 (4.4) kg/m^2 followed for 8 years with 4 measurements of GFR, and another cohort of type 2 diabetic patients with overt diabetic nephropathy n=227, 167 males, mean (SD) age 57 (8), BMI 30.0 (5.3) followed for 6.5 (range 3-17) years with 7 (3-22) measurements of GFR.
For patients with microalbuminuria mean (SD) baseline GFR (ml/min/1.73 m^2) was 117 (24) (range 31-178) measured, and 92 (20) estimated (MDRD) or 103 (24) estimated CG ($p<0.001$). The difference between an individually estimated value and measured GFR (the 95% limits of agreement) were -66 to 20 ml/min/1.73 (MDRD) and -59 to 31 (CG). Rate of decline in GFR (mean (SD)) was 4.1 (4.2) ml/min/year measured, and 2.9 (2.8) MDRD or 3.4 (3.2) CG ($p<0.001$).

For patients with overt nephropathy baseline GFR was 84 (30) (range 20-175) measured and 73 (24) MDRD or 81 (28) CG with 95% limits of agreement of -47 to 25 (MDRD) and -39 to 33 (CG) ($p<0.05$). Rate of decline in GFR was 5.2 (4.1) measured, and 4.2 (3.8) MDRD, and 4.6 (4.1) CG ($p<0.001$).
Conclusion: glomerular filtration rate is significantly underestimated with wide limits of agreement by the MDRD equation as well as by the Cockroft-Gault formula. Particularly in microalbuminuric (hyperfiltering) patients. The rate of decline in GFR is also significantly underestimated with both equations. This makes the GFR estimations unacceptable for monitoring kidney function in individual or groups of type 2 diabetic patients.

Performance and limits of MDRD and Cockcroft-Gault (CG) formulas according to age, gender and GFR levels.

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Age is one of the parameters that are taken into account in the MDRD and CG formulas. However, in older subjects, recommended formulas remain to be validated. To assess the accuracy of the MDRD abbreviated formula and CG formula (corrected for BSA) we compared the results of estimated GFR with true GFR values obtained from 51Cr-EDTA clearance in 2,095 consecutive independent subjects. 595 of them were 65 years or older (362 males, 233 females), 1,500 were under 65 years of age (870 males, 630 females). The population was also subdivided in two groups depending on measured GFR values: "High GFR" ≥ 60 mL/min/1.73m2 (n = 1,044) or "Low GFR" < 60 mL/min/1.73m2 (n= 1,051).
Bias is defined as the mean difference between Estimated and Measured GFR. Precision is expressed as one standard deviation of bias. Data are presented in absolute (mL/min/1.73m2) and relative (%) difference to measured GFR.

Absolute ($mL/min/1.73m^2$)	MDRD GFR		CG GFR	
Relative (%)	Male	Female	Male	Female
High GFR				
Age ≥ 65 yr.	-5.9 / 12.1	-1.6 / 11.5	-14.5 / 10.4	-10.7 / 12.2
	-8.0 / 16.2	*-1.0 / 14.2*	*-19.7 / 13.4*	*-12.4 / 13.5*
Age < 65 yr.	-0.6 / 16.4	-6.1 / 19.3	3.2 / 17.1	2.5 / 22.2
	-0.2 / 18.6	*-5.4 / 20.7*	*4.1 / 19.2*	*3.7 / 22.7*
Low GFR				
Age ≥ 65 yr.	0.5 / 6.7	1.2 / 8.2	-2.3 / 7.2	-0.1 / 8.0
	5.6 / 31.4	*7.6 / 34.1*	*-0.2 / 32.0*	*7.6 / 36.2*
Age < 65 yr.	1.4 / 8.2	2.3 / 10.7	5.9 / 8.8	8.7 / 10.5
	7.0 / 27.5	*10.5 / 41.6*	*24.8 / 35.2*	*32.8 / 43.6*

First, CG formula provides a wide underestimation of GFR in older subjects with normal or near normal renal function. Second, no age-dependent difference in bias was observed in patients with low GFR using MDRD estimation, by contrast to CG formula results.

M Froissart et al. KDIGO CKD Controversies Conference, Amsterdam, 2004

Performance and limits of MDRD and Cockcroft-Gault (CG) formulas according to Body Mass Index (BMI) and gender.

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Weight and height are parameters that are related to daily creatinine production as they are linked to muscular mass. They are taken into account, directly or indirectly (through integration of BSA normalization), in estimated GFR. To assess the accuracy of the MDRD abbreviated formula and CG formula (corrected for BSA) we compared the results of estimated GFR with true GFR values obtained from 51Cr-EDTA clearance in 2,095 consecutive independent subjects. The population was subdivided into 4 groups depending on calculated BMI (in kg/m^2) : < 18.5, 18.5 to 25, 25 to 30, and > 30. A second analysis, in order to detect differences between BMI groups depending on gender was also performed.
Bias is defined as the mean difference between Estimated and Measured GFR. Precision is expressed as one standard deviation of bias. Data are presented in absolute ($mL/min/1.73m^2$) difference to measured GFR.

Bias / Precision	BMI groups			
	< 18.5	18.5 – 25	24 – 30	> 30
Overall (n)	94	1,010	712	279
MDRD	12.2 / 24.8	-0.7 / 13.7	-2.4 / 11.4	-2.6 / 11.6
CG	*6.4 / 17.7*	*-0.4 / 14.4*	*1.8 / 14.0*	*9.2 / 18.7*
Males (n)	38	550	494	150
MDRD	12.1 / 16.3	2.1 / 12.1	-2.7 / 11.5	-2.8 / 9.9
CG	*5.1 / 14.1*	*1.0 / 13.3*	*0.4 / 13.7*	*6.4 / 13.8*
Females (n)	56	460	218	129
MDRD	12.3 / 29.4	-4.1 / 14.7	-1.8 / 11.1	-2.4 / 13.4
CG	*7.4 / 19.8*	*-2.0 / 15.4*	*5.0 / 14.2*	*12.5 / 22.7*

Biases were of lower magnitude in normal and overweight groups for the two formulas, however in these subgroups the precision was always better using MDRD estimated GFR. MDRD was less biased and more precise in obese subjects than CG formula. MDRD and CG largely overestimated function in underweight subjects.

M Froissart et al. KDIGO CKD Controversies Conference, Amsterdam, 2004

Consequences of the limitations of the MDRD and Cockcroft-Gault (CG) formulas on the K/DOQI CKD classification.

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The K/DOQI guidelines recommend defining a clinical action plan for each patient with CKD, based on the stage of disease as defined by the K/DOQI CKD classification. We evaluated the consequences of the limitations of the MDRD and CG formulas on the classification of CKD patients. The analysis was based on results of GFR determinations (51Cr-EDTA clearance) in 2,095 consecutive independent subjects, whether or not they had kidney damage.
As combining the two formulas has been previously proposed as a research track, an analysis of the performance of the average of MDRD and CG estimation of GFR is also provided.

Subjects with measured GFR (mL/min/1.73m^2)	N	Percentage of subjects who did not change stage when classified by estimated GFR		
		MDRD	CG	Average MDRD and CG
≥ 90 (stage 1)	482	66.8 %	72.2 %	69.5 %
60 – 89 (stage 2)	576	63.7 %	58.7 %	63.5 %
30 – 59 (stage 3)	597	78.1 %	77.9 %	80.1 %
15 – 29 (stage 4)	312	78.8 %	67.6 %	74.4 %
< 15 (stage 5)	128	64.8 %	43.0 %	55.5 %

For subjects with GFR ≥ 90 mL/min/1.73m2, the CG formula was slightly more accurate than the MDRD one, but for all other GFR levels, more subjects were classified in the proper stage by the MDRD formula than by the CG one. Using the average values of both formulas to estimate GFR did not improve significantly the accuracy of the prediction.

M Froissart et al. KDIGO CKD Controversies Conference, Amsterdam, 2004

Assessment of renal function in CKD stage 4 and 5

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1. We have previously examined the validity of renal Kt/V as marker for initiation of dialysis therapy (M.K. Kuhlmann**,** M. Heckmann, W. Riegel, H. Köhler: Evaluation of renal Kt/V as a marker of renal function in predialysis patients. Kidney Int 60:1540-1546, 2001).

2. More recently we have studied the validity of the various MDRD equations for prediction of GFR in CKD stage 4 and 5 using inulin clearance as gold standard.
Methods: A total of 50 measurements of inulin clearance (Cin) were performed in 27 patients with GFR < 25 ml/min/1.73m2 and results compared with GFR predicted from the 6-, 5-, and 4-variable MDRD equations and the original as well as modified Cockcroft-Gault formulas. **Results:** Inulin clearance was < 22 ml/min/1.73m² in all and < 10 ml/min/1.73m² in 35 % of patients. Mean values of the four MDRD equations did not differ from Cin and from each other. Inulin clearance correlated best with averaged creatinine and urea clearance (Ccr/ur) and the 6-variable MDRD equation (MDRD#6). Each of the MDRD equations showed a systematic bias towards overestimating GFR in subjects with Cin < 15 ml/min/1.73m². Diagnostic validity to identify patients with Cin < 10.5 ml/min/1.73m² to be considered for dialysis initiation was highest for MDRD#6 and acceptable for the widely used 4-variable MDRD equation (MDRD#4).
Conclusions: All MDRD equations systematically overestimate true renal function in patients with GFR < 15 ml/min/1.73m2. Although highest accuracy, precision and diagnostic performance was found for MDRD#6, the 4-variable MDRD equation is recommended for estimation of GFR in stage 4 and 5 CKD.

3. We have further developed a unique software tool for nephrologists that allows documentation and longitudinal evaluation of renal function or dialysis dose (HD and PD) in patients with CKD. The program allows estimation of GFR from MDRD equation, as well as measurement of urea, creatinine, averaged urea-creatinine clearances, as well as nPCR in any stage of CKD. The windows based program (CKD-PILOT, Authors: M.K. Kuhlmann, W. Riegel, and S. Geberth) is available in English language.