

**KDIGO Controversies Conference on  
Chronic Kidney Disease as a Global Public Health Problem:  
Approaches and Initiatives**

**ABSTRACTS**

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## **SPECTRUM AND ISSUES OF CHRONIC KIDNEY DISEASE IN INDIA**

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Chronic Kidney Disease in an epidemic form in India. From June 2005 to Aug 2006, we prospectively evaluated patients of CKD from various issues point of view particularly pattern of disease, demography and socioeconomic spectrum and risk factor analysis. During study period, 890 patients of CKD were enrolled. Of these, 66.9% were males and mean age of all the patients was  $43.0 \pm 14$  (range 12-85). According to staging of CKD, patients presented in stage 1, 2, 3, 4 and 5 respectively in 10.9%, 12.5%, 22%, 19.6% and 35%. Definite chronic glomerulonephritis was in 4.5%, diabetic nephropathy in 25.8%, hypertensive nephrosclerosis in 14.2%, tubulointerstitial disease other than VUR in 15% and polycystic kidney disease in 4.1% cases. Family history of hypertension, diabetes and CKD in first-degree relatives was found in 8.5%, 17.6% and 3.9% respectively. Distribution of religion was 89% Hindu, 6% Muslim, 0.7% Christian and 3.5% Sikh community. In term of education, illiterate, literate, primary education, secondary education, graduate and postgraduate education was found in 17.4%, 24.9%, 29.7%, 21.2%, 1.4% and 5.5% respectively. 87.3% patients had family income less than 450\$, a cost approximately required for monthly renal replacement therapy (RRT) in India. Of all the patients, source of funding for treatment was self, reimbursement and others in 67.9%, 31.7% and 0.4% cases respectively. 56.9% were vegetarian. Mean height and weight of patients was  $162 \pm 10.8$  cms and  $62.8 \pm 14.7$  Kg respectively. Urinary protein in spot sample was found in +, ++, +++, +++++ in 28%, 34%, 12% and 3.6% cases respectively. Our data shows that in India, CKD is common in young male with lower socioeconomic group of the society who has to self-finance the treatment of CKD. This has serious social implications and society should gear to handle the problem of increasing CKD population currently and in years to come.

**RAFAEL BURGOS-CALDERON, MD**

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## **A PRACTICAL SYSTEMATIC MULTIFACTOR SPECIFIC RISK – FACTOR APPROACH FOR CRONIC KIDNEY DISEASE MANAGEMENT**

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The Systematic Approach for Management of Patients with Chronic Kidney Disease (Spanish ASERC) sets forth a vital tool to face the epidemic of Chronic Kidney Disease (CKD). It is clear that today treating chronic kidney disease patients with diverse therapeutic regimes is not enough, and that it is necessary to demonstrate that CKD remission and/or regression can be attained. We strongly believe that this can be accomplished if an orderly and practical follow up model could be put in practice.

ASERC elements can be listed as follows:

First, we should adopt recommendations from the K/DOQI guidelines:

1) Definition of the Chronic Kidney Disease. 2) Serum creatinine is not a reliable test to estimate glomerular filtration rate (GFR). 3) The ratio (protein/albumin)/creatinine in the urine can substitute protein/albumin 24-hr collection. 4) Use of the following GFR prediction formulae: Cockcroft and Gault or MDRD. 5) Categorize patients according to their stages using the National Kidney Foundation's and/or Puerto Rico's classification.

The Second element is the use of the matrix of classification, regression and remission in CKD patients follow-up.

The Third element consists in the adoption and use of a CKD remission and regression progress note.

In that document, we list most of risk factors associated with progression of chronic kidney disease, establishing a plan of action for each one. In our view, the Systematic Approach and the three elements mentioned above can play a rational and organized role in the follow up of chronic kidney disease patients.

BLANCHE CHAVERS, MD

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## **CARDIOVASCULAR DISEASE IN PEDIATRIC CHRONIC DIALYSIS PATIENTS**

Chavers BM, Shuling L, Collins AJ, Herzog CA  
Kidney Int 62:648-653, 2002.

Medicare incident pediatric (< 20 years) dialysis patients from 1991 to 1996 were identified from the United States Renal Data System. Study endpoints included development of arrhythmia, valvular heart disease, cardiomyopathy, or cardiac arrest, all causes of death, and cardiac-related death. The patient population included all children younger than 20 years old who survived at least 90 days after starting dialysis and who were Medicare eligible at day 90 after the first day of ESRD service. Each cohort was followed from day 91 of ESRD to December 31, 1998. A study endpoint was documented the first time it appeared in the part A or part B claims diagnosis codes. Patients were excluded from the analysis if they underwent transplantation but returned to dialysis within 90 days after the first day of ESRD service. Patient demographic data included age, sex, race or ethnic group, and primary cause of ESRD. Primary renal diagnoses were grouped into four categories: glomerulonephritis, structural abnormalities, hypertension, and other. Statistical analyses were performed using the Poisson regression model and chi-square test. Eligible for inclusion were 1,454 children, 452 (31.1%) of whom developed a cardiac-related event. Arrhythmia was the most common event (19.6%) compared with valvular disease (11.7%), cardiomyopathy (9.6%), and cardiac arrest (3%). Arrhythmia and valvular heart disease incidence were increased in 15-19 year olds ( $p<0.0001$  for both), females ( $p=0.004$ ,  $p=0.03$ ) and Blacks ( $p<0.0001$ ,  $p=0.002$ ). Cardiomyopathy incidence was increased in Blacks ( $p=0.001$ ) and tended to be increased in females ( $p=0.053$ ). The adjusted annual cardiomyopathy rate during the first 3 years increased between 1991 and 1996 ( $p=0.003$ ). Death occurred in 107 patients, and 41 (38%) were cardiac deaths. This study showed that cardiomyopathy incidence is increasing in pediatric chronic dialysis patients. Black, female, and adolescent children have increased risk for cardiovascular disease.

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## **PREVALENCE OF ANEMIA IN ERYTHROPOIETIN-TREATED PEDIATRIC AS COMPARED TO ADULT CHRONIC DIALYSIS PATIENTS**

Chavers BM, Roberts TL, Herzog CA, Collins AJ, St. Peter WL  
Kidney Int 65:266-273, 2004

We evaluated prevalent hemodialysis patients (0 to 19 years, pediatric: N=1,692; adult: N=352,291) and peritoneal dialysis patients (pediatric: N=597; adult: N=39,136) treated with recombinant human erythropoietin (rhuEPO) from 1996 to 2000. Anemia was defined as a hemoglobin level < 11 g/dL. Mean annual hemoglobin values were calculated by modality, age, sex, and race. Among hemodialysis patients, mean annual hemoglobin values less than 11 g/dL were present in pediatric and adult patients during 54.1% versus 39.8% patient years, respectively ( $P<0.0001$ ); for peritoneal dialysis patients, 69.5% versus 55.1% ( $P<0.0001$ ). Mean hemoglobin values increased over time and in 2000 were 11.2, 11.5, 10.8, and 11.2 g/dL for pediatric and adult hemodialysis and peritoneal dialysis patients. Pediatric hemodialysis patients received intravenous iron less frequently than adults (66.3% versus 82.5% patient years;  $P<0.0001$ ). We concluded that hemoglobin values in rhuEPO-treated pediatric dialysis patients lagged behind those of adult patients, with pediatric patients achieving target hemoglobin values only a minority of the time (45.9% and 30.5% patient years, respectively, for hemodialysis and peritoneal dialysis). Trends show recent improvement in anemia treatment of children on dialysis. Still, further attention to and analysis of rhuEPO and iron therapy in pediatric dialysis patients is warranted.

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## **PREVALENCE OF DECREASED KIDNEY FUNCTION IN CHINESE ADULTS AGED 35 TO 74 YEARS**

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**BACKGROUND:** Chronic kidney disease (CKD) is a major public health burden in Western countries but little is known about its impact in developing countries. We estimated the prevalence and absolute burden of CKD in the general adult population in China.

**METHODS:** A cross-sectional survey was conducted in a nationally representative sample of 15,540 Chinese adults aged 35 to 74 years in 2000 and 2001. Serum creatinine was measured using the modified kinetic Jaffe reaction method at a central laboratory calibrated to the Cleveland Clinic Foundation laboratory. Glomerular filtration rate (GFR) was estimated using the simplified equation developed by the Modification of Diet in Renal Disease study. CKD was defined as an estimated GFR <60 mL/min/1.73m<sup>2</sup>.

**RESULTS:** Overall, the age-standardized prevalences of GFR 60 to 89, 30 to 59, and <30 mL/min/1.73m<sup>2</sup> were 39.4%, 2.4%, and 0.14%, respectively, in Chinese adults aged 35 to 74 years. The overall prevalence of CKD (GFR <60 mL/min/1.73m<sup>2</sup>) was 2.53%, representing 11,966,653 persons (1.31% or 3,185,330 men and 3.82% or 8,781,323 women). The age-specific prevalence of CKD was 0.71%, 1.69%, 3.91%, and 8.14% among persons 35 to 44, 45 to 54, 55 to 64, and 65 to 74 years old, respectively. The age-standardized prevalence of CKD was similar in urban (2.60%) and rural (2.52%) residents but was higher in south China (3.05%) than in north China (1.78%) residents.

**CONCLUSION:** Although the prevalence of CKD in China was relatively low, the population absolute burden is substantial. These data warrant a national program aimed at detection, prevention, and treatment of CKD in China.

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**Title:** Serum Cystatin C GFR Estimation Equation: Pooled Analysis of 3134 Individuals

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**Background:** There has been a great deal of interest in using serum cystatin C (Scys) as a measure of kidney function.

**Methods:** We developed equations for estimating GFR based on Scys alone and in combination with serum creatinine (Scr) in 2/3 of the MDRD, AASK, CSG participants (development sample; n=1935), and validated them in the remainder (internal: n=761) and in a Paris clinical population (external: n=438). GFR was measured as urinary clearance of <sup>125</sup>I-iothalamate (51Cr-EDTA in Paris) along with calibrated Scr, Scys (Dade Behring), and participant characteristics.

**Results:** Mean GFR, Scr and Scys were 49 (5<sup>th</sup> -95<sup>th</sup> percentile 15-97) ml/min/1.73m<sup>2</sup>, 2.0 mg/dL and 1.8 mg/L, respectively. The table shows the bias, precision (root mean square error, RMSE) and accuracy (percentage of measured GFRs within 30% of the estimate) for three equations (eGFR=252\*Scr<sup>-1.14</sup>\*Age<sup>0.29</sup>\*0.77 if female\* 1.21 if Black (similar results with abbrev. MDRD equation); eGFR=76.7\*Scys<sup>-1.18</sup>; eGFR=181\*Scr<sup>-0.62</sup>\*Scys<sup>-0.60</sup>\*Age<sup>-0.20</sup>\*0.84 if female\*1.12 if Black). In other equations with Scys but not Scr, the age, sex and race coefficients were significant but 2 to 4 fold smaller. Average magnitude of errors on a % basis were constant over the GFR range studied.

**Conclusion:** We present a GFR estimation equation with Scys alone based on 1935 individuals with similar precision to an equation utilizing Scr and demographic variables. Combining Scr, Scys can improve GFR prediction compared to either analyte alone but requires inclusion of age, sex and race.

eGFR Model Variables	Bias (Median %)	Precision (RMSE)		Accuracy (% within 30%)	
	Validation	Develop-ment	Validation	Develop-ment	Validation
	Internal, External		Internal, External		Internal, External
N=	761, 438	1935	761, 438	1935	761, 438
logScr + age + sex + race	1, 7	0.23	0.21, 0.23	84.3	85.0, 83.3
logScys	3, -10	0.23	0.25, 0.25	82.9	82.7, 79.5
logScr + logScys + age + race + sex	1, 1	0.20	0.19, 0.19	89.3	90.7, 90.0

**Title:** Effect of Differences Between Serum Cystatin Assays on GFR Estimation

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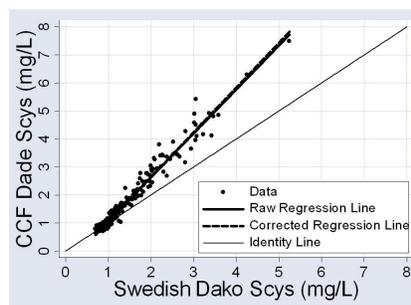
**Background:** Several equations have been published for estimating GFR (eGFR) from serum cystatin C (Scys). However little data are available are how different Scys assays compare to each other and what impact differences would have on GFR estimation.

**Methods:** Plasma frozen at -80C on 200 individuals and linear regression were used to compare the Scys DakoCytomation PETIA assay on the Hitachi Modular P (Sweden, Feb-Oct 2003) to Scys Dade Berhring PENIA on the BNII Nephelometer, the only FDA approved Scys assay in the US (Cleveland Clinic Foundation laboratory, Oct 2005). Equations for eGFR=83.9\*Dako Scys<sup>-1.776</sup> developed in 451 adults in Sweden and eGFR=76.7\*Dade Scys<sup>-1.18</sup> developed in 1,935 adults in the CKD-EPI collaboration were compared.

**Results:** Mean Scys differed substantially between the Swedish Dako (1.51 mg/L) and CCF Dade (1.87 mg/L) assays (difference 0.35 (s.e. 0.03)). The values were highly correlated (R<sup>2</sup>= 0.96, Figure) with measurement error adjusted calibration equation of CCF Dade Scys = -0.554 + 1.598\* Swedish Dako Scys. The table shows the impact on GFR estimation. A comparison of published equations using the Dade assay reveals differences as well.

**Conclusion:** The Dade and Dako Scys assays differ substantially. Differences between equations for estimating GFR are partly but not completely explained by assay differences.

	Dako Equation	Dade Equation	Dako Equation Calibrated to Dade Assay
Scys, mg/dl	eGFR Value Corresponding to Scys, mg/dl		
0.5	268	174	169
1.0	84	77	88
2.0	26	34	38
4.0	8	15	15
eGFR	Cystatin Value Corresponding to Given eGFR		
15	2.8	4.0	3.9
30	1.8	2.2	2.4
60	1.2	1.2	1.4



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## **INCIDENCE OF CARDIOVASCULAR DISEASE (CVD) AND RATE OF RENAL FUNCTION LOSS IN K/DOQI STAGES I TO III OF CHRONIC KIDNEY DISEASE (CKD)**

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Early detection of CKD is important due to the associated risks of CVD and accelerated renal function loss. K/DOQI staging has been advocated to identify subjects with CKD, with stage III generally receiving more attention than stages I and II, because of the more impaired eGFR. We investigated whether this is appropriate, and compared the incidence rates (IR) of CVD in subjects with stages I, II (according to K/DOQI defined by eGFR and microalbuminuria (MA)) and III (according to K/DOQI defined by eGFR only). We used data of the PREVEND study, an observational cohort study performed in the Netherlands. IR s are given per 1,000 person-yrs.

Prevalence of CKD stage I-III and demographics are shown in the table below. Median follow-up was 7.3 yrs. The IR s of CVD were significantly higher in subjects with stage I-III CKD (16.9, 22.8 and 22.5, resp.) than in subjects with no CKD (7.1) (all  $p < 0.001$ ). Using subjects with no CKD as reference, the age- and sex-adjusted hazard ratios (HR(95%CI)) for CVD for stage I-III CKD were 2.2 (1.5-3.2), 1.6 (1.3-2.0) and 1.3 (1.0-1.7), resp.

When stage III CKD was subdivided according to absence or presence of MA, the age- and sex-adjusted HR s for CVD were 1.0 (0.7-1.5) and 1.7(1.2-2.4), resp., whereas the annual change in eGFR during follow-up in these two groups (calculated by linear regression analysis using three sequential eGFR measurements over time) was +0.16 1.22 versus -0.50 1.21 mL/min/1.73m<sup>2</sup>/yr, resp. ( $p=0.001$ ).

In conclusion, screening for K/DOQI stages I and II successfully detects subjects at risk for CVD, and should in that respect get equal attention as screening for stage III. Furthermore, K/DOQI stage III, according to the current definition, identifies only subjects with increased risk for CVD or renal function loss if there is also MA present. We therefore propose that for defining stage III CKD, besides the eGFR value, an additional criterion asking for presence of MA is needed.

	<b>No CKD</b>	<b>Stage I</b>	<b>Stage II</b>	<b>Stage III</b>
N	6906	243	856	491
Age, yr (SD)	47 (12)	48 (12)	56 (12)	63 (9)
Male, %	49	66	64	38

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Urinalysis, specific proteins and creatinine standardisation are among the research interests of Dr. J. Delanghe (Dept. of clinical chemistry, University Hospital Gent, Belgium). At present, the issue of creatinine standardisation and its consequences 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. 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. J. Delanghe chairs a European working group on creatinine standardisation and its clinical consequences. It is clear that the MDRD recommendations and the planned introduction of NIST 967 standard for creatinine have some unwanted side effects (e.g. Cockcroft and Gault based drug dosage schemes, formulas for estimating GFR in children). Especially in the younger age groups (1-3 years), the variations between creatinine methods are still very pronounced

References:

Clin Chem 2003; 49: 163;49:1011-1014; Accreditation and Quality control 2005; 10: 15-19.

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## **THE IMPORTANCE OF NEPHROLOGY IN PUBLIC HEALTH (PROGRAM FOR SURVEILLANCE AND CONTROL OF CHRONIC DISEASES)**

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As recently as April 2006, CDCs (Centers for Disease Control and Prevention) in the United States of America<sup>1</sup> placed chronic renal disease in the center of public health debate requiring an action plan from country governments. In this way, it was acknowledged in their vision that prevention efforts are yet undeveloped.

For many years now, clinical nephrology has been fostering the need to control the impact of permanent renal disease within the public health environment.

The lack of a systematized control provided through a measurable program has greatly impacted on the level of hospital expense since they have increased their case-mix risk, family economies deteriorate and health care pays for a higher morbimortality that could be avoided with better surveillance and epidemiological control.

However, nephrology associations have paved the way in this effort. The "Sustainable and Tenable Renal Health Model" from the SLANH has already been implemented in 11 countries in the Latin American region.<sup>2</sup>

This model incorporates Wagner's<sup>3</sup> managed care "Model to Improve Chronic Disease Care", and is enhanced with public health proposals that establish strategies for cardiovascular, cerebral, renal and endocrine-metabolic health.

This is a novel proposal for surveillance and epidemiological control of prevalent chronic diseases in primary health care and in first level of attention, since it integrates medicine and clinical nephrology with public health.

The model favors control of diabetes, hypertension, obesity and dislipemia through systematic follow ups that protect against the progression of endothelium damage, which is a marker of the evolution towards multiorganic failure.

Planned in the Logical Frame and the Matrix of Allocation of Activities and Resources<sup>4</sup>, it facilitates its financing as a national program or with external financing.

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<sup>1</sup> Schoolwerth, Anton C., Engelgau, Michael M, Hostetter, et al. Chronic Kidney Disease: A Public Health Problem That Needs a Public Health Action Plan. Preventing Chronic Disease. Volume 3: No. 2, April 2006

<sup>2</sup> Argentina, Brasil, Chile, Colombia, Ecuador, México, Paraguay, Perú, Puerto Rico, Uruguay y Venezuela

<sup>3</sup> Wagner EH. Chronic disease management: What will it take to improve care for chronic illness? Effective Clinical Practice. 1998;1:2-4.

<sup>4</sup> Depine Santos: Guidelines to a Cost-Efficient Assignment of Activities and Resources in Primary Health Attention. UNDP-International Financial Health Unit. Health Ministry, Argentina, 2002

MATTHIAS GIRNDT, MD

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## **T CELL AND MONOCYTE FUNCTION IN CHRONIC RENAL DISEASE**

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Patients with chronic renal failure suffer from specific immune incompetence, e.g. against viral diseases such as hepatitis B, while several antigen-unspecific immune functions such as cytokine secretion by monocytes are upregulated. Therefore, these patients experience chronic course of viral disease, frequent infectious complications, reduced vaccination efficacy, and enhanced atherosclerosis due to inflammatory overactivation. Our group was the first to study inflammatory activation of monocytes in kidney failure at a single cell level by flow cytometry. We showed that monocytes are heterogeneous in their cytokine production (similar to their heterogeneity as defined by surface markers CD14 and CD16). Those with the highest production of cytokines are preferentially removed from circulation during a dialysis session. Intracellular detection of cytokines at single cell level has several advantages over measurement of plasma cytokines since there is no dependence on the relative cell number in circulation and on residual renal function.

Cytokine production is partially determined by genetic polymorphisms, which seem to be particularly relevant for the patient with renal failure and inflammatory activation. Our group showed a predictive role for a polymorphism of the anti-inflammatory cytokine IL-10 for both, immune function and cardiovascular mortality. Recently, we could prove a role of a polymorphism of the pro-inflammatory IL-6 for renal anemia and the need for erythropoetin.

Specific immune activation against viral infections depends on a complex system of interactions between antigen-presenting cells and T lymphocytes. We demonstrated that chronic kidney disease influences the expression of the signalling molecule CD86 on monocytes thus leading to reduced specific activation of T lymphocytes. This finding is closely related to nonresponse after hepatitis B vaccination among these patients.

LEE HEBERT, MD

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## **ALLHAT HAS DESIGN FLAWS THAT MAY HAVE BIASED THE STUDY'S OUTCOME IN FAVOR OF THE DIURETIC COHORT**

LA Hebert, BH Rovin, CJ Hebert

The Ohio State University Department of Medicine and Cleveland Clinic Department of General Internal Medicine

ALLHAT is the only modern hypertension trial to deliberately recruit hypertensives with cardiovascular (CV) disease, and then use diuretic as one of the randomized interventions. This is a design flaw because CV disease patients are especially vulnerable to fluid overload, which can exacerbate their hypertension, heart failure, or angina. This flaw advantaged the diuretic cohort because the other randomized monotherapies, lisinopril (ACEI), and amlodipine (CCB), are not recommended as monotherapies to manage fluid overload. Also, ACEI's remarkable CV benefits were demonstrated when ACEI was combined with diuretic, if needed. Thus, ALLHAT's design prevented ACEI's optimum use.

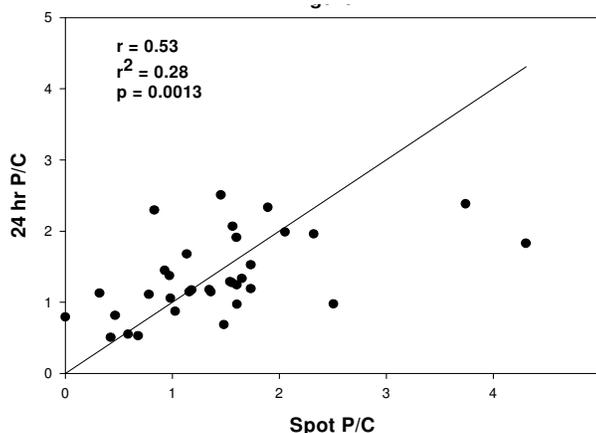
ALLHAT's other design flaw is that its protocol required advancing randomized monotherapy to achieve the blood pressure (BP) goal. To illustrate how bias is introduced, consider this scenario: Hypertension worsens. Incipient fluid overload is suspected. The blinded monotherapy is advanced hoping it is diuretic. Unfortunately, it is ACEI or CCB. Fluid overload and hypertension worsen. Weeks later, the patient returns with stroke, MI, or CHF. Such endpoints should be regarded as artifacts of ALLHAT design because in routine clinical care, likely they would have been avoided by timely diuretic use.

ALLHAT's design gave diuretic a monopoly on BP and volume control. Still, diuretic could not lower mortality or MI rate (ALLHAT's primary endpoints) better than ACEI. Likely diuretic's metabolic dysfunctions, which increase CV risk, negated the benefits bestowed by diuretic's "monopolies". Diuretic should not be initial therapy for all hypertensives. A better evidence-based strategy is ACEI alone, or combined with diuretic if needed.

## SPOT URINE PROTEIN/CREATININE RATIO (P/C) IS AN UNRELIABLE METHOD FOR ESTIMATING 24-HR PROTEINURIA (P) FOR MOST CLINICAL PURPOSES

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P is a modifiable risk factor and the strongest predictor of GFR decline in CKD. Accurately assessing P change, particularly in the range of 1 to 3 g/d, is the usual clinical need. The gold standard is 24-hr P, but this is inconvenient. Spot urine P/C is convenient and shows high correlation with 24-hr P. On this basis, KDOQI now recommends spot urine P/C. However, the high correlation coefficients appear to be the result of comparing spot P/C and 24-hr P over a very wide range, a range not usually encountered in individual patients (AJKD 47:8-14,2006). This study examined this issue by analyzing 649 paired spot and 24-hr urine collections submitted by an SLE GN cohort (N = 74) followed long term in the Ohio SLE Study. From this data set 55 pairs were selected randomly to cover a wide-range of 24 hr P/C ratios (0.06 to 6.5), and in which the 24-hr collections were at least 75% of a complete collection (based on Cockcroft-Gault), which provides an accurate estimate of the P/C ratio of a complete 24-hr collection (data not shown). Consistent with previous studies, we found that over the entire range of P/C values there was strong linear correlation between spot and 24-hr urine P/C ( $r = 0.78$ ,  $r^2 = 0.61$ ,  $p < 0.0001$ ). However, over the ranges more relevant to individual patient assessment (see figure), correlation was statistically significant ( $p=0.0013$ ) but agreement between spot and 24-hr urine P/C ratios was weak ( $r^2 = 0.28$ ). Conclusions: For optimum CKD management, P should be assessed from the P/C ratio of specimens submitted as 24-hr collections, not spot urine P/C. A further advantage of 24-hr testing is the ability to monitor NaCl and protein intake, which is important in CKD management.



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## ESTIMATION OF GLOMERULAR FILTRATION RATE BY THE MDRD EQUATION MODIFIED FOR JAPANESE PATIENTS WITH CHRONIC KIDNEY DISEASE

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Japanese CKD Initiatives, Japanese Society of Nephrology

Accurate estimation of glomerular filtration rate (GFR) is crucial for detection of chronic kidney disease (CKD) in clinical practice. Especially, to distinguish CKD stage 3 from CKD stage 2, the GFR must be accurate around 60ml/min/1.73m<sup>2</sup>. Cockcroft-Gault equation and MDRD abbreviated equation have been used for this purpose in Japan. In the present study, the equations originally developed for Caucasian population were tested in Japanese CKD patients, and modified with the Japanese coefficient determined by the data of inulin clearance (C<sub>in</sub>) from Japanese 248 CKD patients. For determination of the Japanese coefficient, the sum of squared errors of estimate (SSE) was used. Thus, serum creatinine values of enzymatic method in the present study were calibrated to values of non-compensated Jaffé method by adding 0.207mg/dl, which was similar to the difference of serum creatinine levels between the mean-value of the college of American Pathologists (CAP) survey and the enzymatic method in Japan. We obtained a coefficient, 0.881 and determined the modified MDRD equation as follows.

$$eGFR \text{ (mL/min/1.73 m}^2\text{)} = 0.881 \times 186.3 \times \text{Age}^{-0.203} \times \text{S-Cr}^{-1.154} \text{ (if female } \times 0.742\text{)}$$

The MDRD equation modified with Japanese coefficient (0.881 × MDRD) determined for Japanese CKD patients yielded lower mean difference and higher accuracy for GFR estimation in appended Fig. 1. In particular in C<sub>in</sub> 30-59 mL/min/1.73m<sup>2</sup>, the mean difference was significantly smaller with 0.881 × MDRD than that with 1.0 × MDRD (1.9 vs 7.9 mL/min/1.73m<sup>2</sup>, p<0.01), and the accuracy was significantly higher, with 60% vs 39% of the points deviating within 15%, and 97% vs 87% of points within 50%, respectively (both p<0.01). The validation with different data from 264 CKD patients showed the correlation between eGFR and C<sub>in</sub> was better by 0.881 × MDRD than 1.0 × MDRD. In C<sub>in</sub> less than 60 mL/min/1.73 m<sup>2</sup>, the accuracy was significantly higher, with 85% vs 69% of the points deviating within 50% (p<0.01), respectively. The mean difference was also significantly smaller (p<0.01).

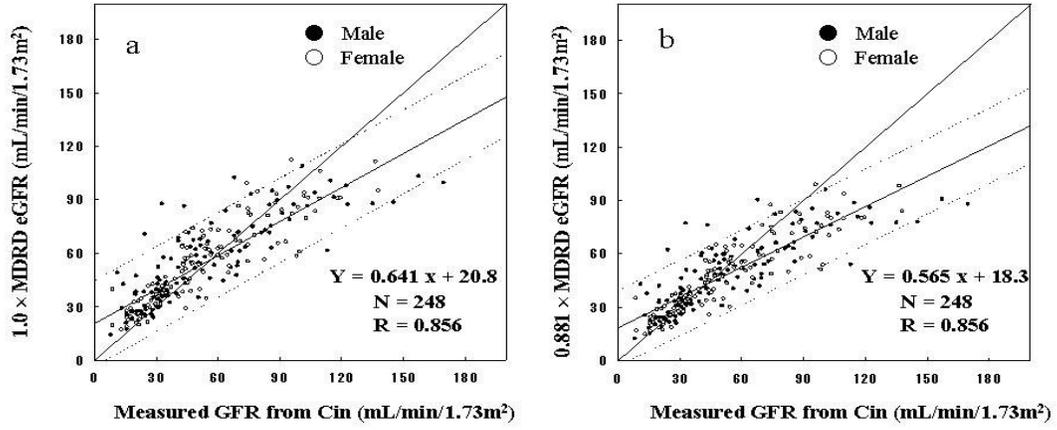
Recently, Levey et al modified the abbreviated MDRD equation by calibrating MDRD study creatinine to IDMS traceable value and re-expressed MDRD equation as follows:

$$eGFR = 175 \times \text{Cr}^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \text{ (if female)}$$

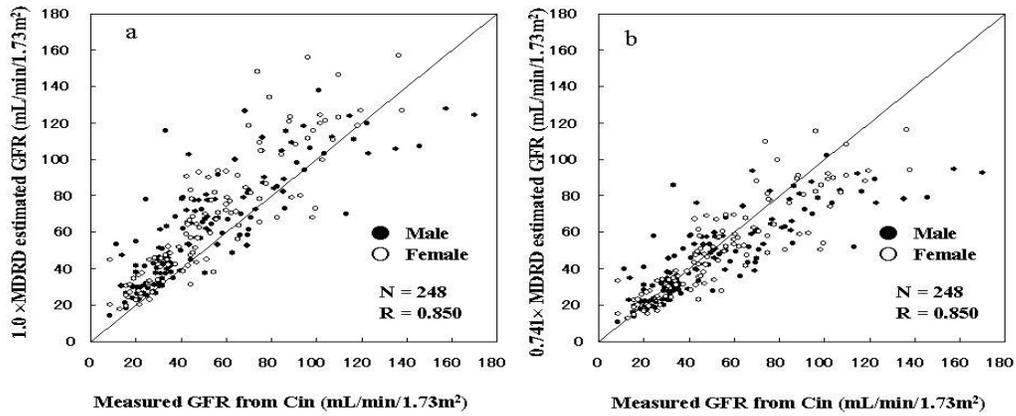
We calculated eGFR by the above new equation inserted the serum creatinine measured by enzymatic method and plotted against measured GFR by inulin clearance (n=248), which is shown in appended Figure 2. When we added a coefficient, 0.741 to the new equation, the coefficient again improved the eGFR at GFR less than 60ml/min/1.73m<sup>2</sup>.

In conclusion, the modification with Japanese coefficient multiplier improved the accuracy of GFR estimation by the abbreviated MDRD equation as well as by the new MDRD equation, particularly in patients with CKD stage 3 and stage 4. The equation is still non-optimal for estimation within Japanese even after the modification, since it underestimates GFR above 60 ml/min/1.73 m<sup>2</sup>. Thus, development of a new equation is strongly suggested for improved accuracy in estimation for Japanese and for Asian population in near future.

**Figure 1**



**Figure 2**



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REYKJAVÍK, ICELAND

## CKD IN EUROPE (ICELAND)

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**Background:** Iceland has a population of approximately 300,000 and provides universal coverage for health care, including unrestricted access to RRT. Nevertheless, the incidence of treated ESRD, 70/million/year, is low compared to many Western nations, and interestingly, few diabetics have entered RRT.

**Methods:** To examine if a low prevalence of CKD may explain the low incidence of ESRD, we have studied the prevalence of this disorder in the Icelandic population, comparing different equations used for defining CKD. We also have examined the progression of kidney disease in a limited number of subjects. In addition, we have studied the incidence of diabetic nephropathy in patients with type 1 diabetes in Iceland.

**Results:** In a cohort of 9,229 males and 10,027 females, aged 33 to 85 years, we found that different eGFR equations performed differently in defining CKD. Using the modified MDRD equation, age-standardized prevalence of eGFR <60 ml/min/1.73 m<sup>2</sup> was 4.7% for men and 11.6% for women. An additional 2.4% of men and 0.9% of women had proteinuria. Among those with serum creatinine >150 µmol/L, 70% had progressive decline in renal function, 45% developed ESRD, and 30% received RRT. The incidence of diabetic nephropathy was 40% in patients with type 1 diabetes after 30-40 years of follow-up.

**Conclusions:** The low incidence of treated ESRD in Iceland cannot be explained by a low prevalence of CKD nor is the incidence of diabetic nephropathy in Icelandic patients with type 1 diabetes lower than is generally observed. Our studies suggest that a sizeable proportion of subjects with CKD have a favorable prognosis. The progression of CKD needs further studies. Finally, our results suggest that prediction equations may not be reliable enough for use in epidemiological research.

FUJIKO IRIE, MD, PHD

IBARAKI, JAPAN

# **THE RELATIONSHIPS OF PROTEINURIA, SERUM CREATININE, GLOMERULAR FILTRATION RATE WITH CARDIOVASCULAR DISEASE MORTALITY IN JAPANESE GENERAL POPULATION**

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Proteinuria, high serum creatinine and reduced glomerular filtration rate (GFR) have been associated with increased mortality from cardiovascular disease (CVD) and all causes. However, the combined effect of proteinuria with serum creatinine and GFR on CVD or all-cause mortality has not been well investigated.

We conducted a 10-year prospective cohort study of 30,764 men and 60,668 women aged 40-79 years who participated in annual health checkups in 1993. The Cox proportional hazards model was used to estimate the relative risk (RR) after adjusting for age, smoking, and other cardiovascular risk factors.

The multivariable RR (95% confidence interval (CI)) of CVD death for positive vs negative proteinuria was 1.38(1.05-1.79) among men and 2.15(1.64- 2.81) among women. The respective RR for the highest vs lowest creatinine groups ( $\geq 1.3$  vs  $\leq 0.8$  mg/dl for men and  $\geq 1.1$  vs  $\leq 0.6$  mg/dl for women) was 1.56(1.19-2.04) among men and 2.15(1.58-2.93) among women. The respective RR for GFR $<60$  vs  $\geq 100$ ml/min/1.73m<sup>2</sup> was 1.65(1.25-2.18) among men and 1.81(1.39-2.36) among women. For individuals with proteinuria combined by hypercreatininemia or reduced GFR, the risk of CVD death was two-fold higher in men and 4-6-fold higher in women compared to those without proteinuria and with normal creatinine level or GFR. Similar associations were observed for stroke, coronary heart disease, and all-cause mortality.

Proteinuria, and hypercreatininemia or reduced GFR and there combination were significant predictors of CVD and all-cause mortality. (Kidney Int 2006; 69, 1264-1271)

KUNITOSHI ISEKI, MD

OKINAWA, JAPAN

## INCIDENCE AND PREVALENCE OF CKD IN OKINAWA, JAPAN

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Okinawa, Japan, consists of subtropical islands and has the highest prevalence of ESRD. Currently, the prevalence is more than 2500 pmp (total population, 1.36 million), reasons are not clear yet. We have been studying the renal outcome of the screened population in Okinawa.

The Okinawa General Health Maintenance Association, a nonprofit organization founded in 1972, has been conducting community-based health examination annually. Computer-based registry data for the standard analysis are available for the 1983 (n=106171), 1993 (n=143948), and 2003 (n=154019) screenings. CKD was diagnosed by the KDOQI guidelines. Estimated GFR was calculated using the abbreviated MDRD formula. Since there is no known ethnic factor for Japanese, we did not correct the estimated GFR value. Significant changes in the participants' demographics have been observed during the study period. While both systolic and diastolic blood pressure decreased, mean levels of serum cholesterol, triglycerides, and fasting plasma glucose, and the prevalence of overweight and obesity increased.

The details of every ESRD patient treated in Okinawa since 1971 are maintained in an independent registry; the Okinawa Dialysis Study (OKIDS). By the end of 2000, we registered a total of 5246 patients. Using the two registries, we identified screening participants who later entered a dialysis program using the two computer registries. Among the variables studied, dipstick positive proteinuria was the strongest predictor.

The Okinawa screening program provides valuable opportunities for the detection of CKD in the general population. Changes in physician and patient behavior are needed for better management of CKD.

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## ASSOCIATIONS OF CKD WITH INFECTIOUS DISEASE

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Chronic kidney disease (CKD) is a worldwide public health problem with adverse outcomes of kidney failure, cardiovascular disease, and premature deaths [1]. Infection is an important cause of morbidity and mortality among patients with kidney failure, and according to the US Renal Data System (USRDS) registry, is the second leading cause of death following cardiovascular disease [2] [3] [4]. Whereas infectious diseases can affect CKD in term of risk, initiation, progression, and end stage factors, little is known of the impact of CKD on the development and outcome of infectious diseases.

Consequently, there is a need to gain a broader understanding of the association of CKD with infectious diseases, broadly termed, with a particular focus on chronic viral illnesses. It should also be noted that the natural course of infectious diseases might be influenced by coexisting CKD [5] [5] [6] [7] [8] [9] [10]. In this setting, CKD might either affect the host immune response (favorably or unfavorably) or represent a surrogate marker of greater morbidity. Since the majority of clinical trials exploring novel anti-infectious drugs initially exclude patients with CKD [11] [12] [13] [14], treatment of infectious diseases might also be influenced by coexisting CKD. This might be mediated through either the kidney toxicity of anti-infectious drugs, which hampers effective treatment of infectious diseases, or through suboptimal use of anti-infectious drugs, due to coexisting CKD, resulting in over or under exposure to these drugs.

The association of CKD with impaired host cellular and humoral immunity can also result in suboptimal and/or less sustained vaccination immune responses [3] [15]. This impaired immunity calls for the development of a specialized immunization program for the CKD population against some infectious diseases. This has potential regional and global implications for vaccination strategies worldwide.

Finally, existing methods to estimate GFR do not perform well in the setting of chronic infectious diseases such as the human immunodeficiency viral (HIV) infection [16] [17], particularly if superimposed on malnutrition with accompanying abnormal muscle mass and/or low body mass index. This also calls for the need to develop better tools to estimate GFR.

In summary, the CKD-infectious disease axis is a novel research field that warrants further inquiry in the hope of improving global health.

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TAZEEN JAFAR, MD

KARACHI, PAKISTAN

## **MICROALBUMINURIA IS ASSOCIATED WITH MAJOR ELECTROCARDIOGRAPHIC CHANGES IN AN INDO ASIAN POPULATION**

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### **Background:**

Microalbuminuria (MA) is a known predictor of cardiovascular disease (CVD) in European origin populations, but such data are lacking in native Indo-Asian populations, where CVD risks are high. Major electrocardiographic (EKG) changes are predictive of cardiovascular mortality. We determined the association of MA with major EKG changes in the general population of Pakistan.

### **Methods:**

A total of 3143 of 3546 invited subjects aged 40 years or over from twelve randomly selected communities in Karachi participated. MA was defined as albumin excretion  $<300$  mg/g creatinine and  $\geq 17$  mg/g in men and  $>25$  mg/g in women from a single spot morning urine sample. Major ischemia was coded in duplicate on EKG using Minnesota classification. Hypertension was defined as  $BP \geq 140/90$  mm Hg or on antihypertensive medication, diabetes as fasting blood glucose  $\geq 126$  mg/dl or on antidiabetic medication, estimated glomerular filtration rate (eGFR) was calculated using the MDRD Study equation.

### **Results:**

The mean age of subjects was 51.6 (10.8) years. Median (25-75% percentile) urine albumin to creatinine ratio was 4.0 (3.0-8.0) mg/g in men and 6.0 (4.0-11.0) mg/g in women ( $p < 0.001$ ). Prevalence of major EKG changes was 15.8%, hypertension 42.6%, diabetes 20%, eGFR  $<60$  ml/min/1.73 m<sup>2</sup> 15.8%. Prevalence (95% CI) of MA was 9.2% (8.4-11.8%) overall, 14.5% in those with major ischemia, 13.8% among those with hypertension, and 19.5% among those with diabetes and 11.9% among those with eGFR  $<60$ . In a multivariate model, MA was independently associated with major ischemia (OR, 95% CI) (1.45, 1.06-1.98), diabetes (2.81, 2.16-3.66), hypertension (1.79, 1.36-2.35), women (0.69, 0.53-0.89), age (1.03, 1.02-1.04, for each 1 year increase), and eGFR (0.90, 0.84-0.96, for each 10 ml/min/1.73 m<sup>2</sup> increase).

### **Limitations:**

Urine albumin was determined from a single urine collection; presence of hematuria and pyuria was not tested. In addition, the MDRD Study equation for estimation of eGFR, and the classification of EKG changes for prediction of CVD have not been validated in Indo Asians.

### **Conclusions:**

MA is associated with major EKG changes in Indo Asians, independently of hypertension, diabetes, or decreased eGFR.

## USE OF SCREENING TESTS FOR MICROALBUMINURIA IN AN INDO-ASIAN POPULATION

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### Background:

Microalbuminuria (MA) based on 24 hour urine albumin excretion is one of the criteria for chronic kidney disease and a predictor of cardiovascular disease. Indo Asian subjects are at high risk of both, but the validity of simple screening tests, such as urine albumin to creatinine ratio (ACR), and urine albumin concentration (UALB) have not been determined, and given lower urine creatinine excretion levels, the former may be misleading. We compared the use of ACR and UALB for predicting MA in this population.

### Methods:

A total of 577 subjects aged  $\geq 40$  years, 54% of whom were women, were recruited from the general population residing in four randomly selected communities in Karachi, Pakistan. ACR (mg/g of creatinine), and ALB (mg/L) were determined in a spot morning urine sample, and MA (30-300 mg of albumin) in a 24 hour urine collected on the subsequent day.

### Results:

The median (25-75 percentile) of urine albumin excretion was 5.0 (3.6-10.9) mg/day: 5.8 (3.8-13.2) mg/day in men, and 4.6 (3.4-0.9.3) mg/day in women. The overall prevalence (95% CI) of MA was 9.4% (7.2 to 12.0%): 11.0% in men, and 8.0% in women ( $p=0.20$ ). The areas under the receiver operator characteristic (ROC) curves for detection of MA were 0.92 (0.88 to 0.95) and 0.91 (0.86 to 0.94) for UALB in women and men, respectively. The same were 0.95 (0.92 to 0.97) and 0.93 (0.89 to 0.96) for ACR in women and men, respectively. For UALB, the sensitivity and specificity were 50% and 98%, respectively in women, and 71% and 97%, respectively, in men at the conventionally recommended value of 3 mg/dl. The discriminator value of UALB identified in the analysis was 0.6 mg/dl in women (sensitivity of 92%, specificity of 83%), and 1.3 mg/dl in men (sensitivity of 82%, and specificity of 90%). For the ACR, the sensitivity and specificity were 82% and 97%, respectively, in women at discriminator value of 25 mg/g, and 82 and 93%, respectively, at value of 17 mg/g in men.

### Conclusion:

Both UALB and ACR are acceptable tests for population screening for MA in Indo Asians. The existing cut off values for ACR for identification of MA seems reasonable for application in the adult Indo Asian population. However, thresholds for UALB need to be lowered. Those who screen positive with either test should be followed with timed urine samples for confirmation of MA.

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## **THE INCIDENCE OF END-STAGE RENAL DISEASE IN INDIA: A POPULATION-BASED STUDY**

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Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are emerging public health problems in developing countries, and need changes in healthcare policy. ESRD incidence data are not available from large parts of the developing world including South Asia. We report the ESRD incidence in a large urban population in India. ESRD incidence was estimated for four consecutive calendar years (2002-2005) amongst 572,029 subjects residing in 36 of the 56 wards of the city of Bhopal. These subjects are beneficiaries of free healthcare in a hospital established after the 1984 Union Carbide Industrial Accident. Crude and age adjusted incidence rates were calculated. A total of 346 new ESRD patients were diagnosed during the study period; 86 in 2002, 82 in 2003, 85 in 2004 and 93 in 2005. Average crude and age-adjusted incidence rates for were 151 and 232 per million population respectively. The mean age was 47 years, and 58% were males. Diabetic nephropathy was the commonest (44%) cause of ESRD. This study provides the first population-based ESRD incidence data from India and reveals it to be higher than previously estimated. This translates into a large ESRD burden for a nation of over one billion people. Diabetic nephropathy is the leading cause of ESRD. Changes are required in healthcare policy to institute CKD detection and prevention programs as well as efficient resource utilization for ESRD care.

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## **REFERRAL PATTERN OF PATIENTS WITH END STAGE RENAL DISEASE AND ITS IMPACT ON OUTCOME AT A TERTIARY CARE CENTRE IN NORTH INDIA**

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Timely referral of patients with chronic renal failure to a nephrologist is an important determinant of outcome. There is no data on the timing and quality of care before initiation of dialysis in developing countries. All patients referred to our Institute with a diagnosis of ESRD over a 1-year period were evaluated prospectively. Quality of pretransplant care was assessed by patient interviews, referral notes and admission records. Referral duration was classified according to time from first evaluation by a nephrologist to development of ESRD as early (>12 months), intermediate (4 to 12 months) and late (<4 months). Outcomes were recorded as death, lost to follow up (presumed dead), or according to RRT modality. A total of 450 cases (75% males, mean age 43.3±15.8 years) were studied. Diabetic nephropathy (32%), chronic glomerulonephritis (22%), and chronic interstitial nephritis (18% each) were the commonest causes. 329 (73.1%) patients were referred late whereas 17.6% and 9.3% had intermediate and early referrals respectively. The patients in the late referral group were more likely to have uncontrolled hypertension, fluid overload, hyperkalemia, severe acidosis, and 65% required dialysis within 24 hours of presentation. The prevalence of malnutrition was higher, whereas the family income and access to medical reimbursement was lower in this group. The outcome frequencies were: death (5.6%), lost to follow up (59.3%), transplantation (15.1%), hemodialysis (14%), and CAPD (6%). Those who died or were lost to follow up were more likely to be uneducated, have infections, coronary artery disease, underlying lung disease, malnutrition, late referrals and lower family incomes. In conclusion, majority of CKD patients in our study were referred late. Late referral is associated with increased risk of presentation with severe uremic complications, requirement of emergency dialysis, worse metabolic parameters, absent predialysis care and poor socioeconomic status.

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## **MANAGING CHRONIC ILLNESSES – CHRONIC KIDNEY AND CARDIOVASCULAR DISEASE - A 5 YEAR EXPERIENCE OF THE CHRONIC DISEASE OUTREACH PRIMARY PREVENTION PROGRAM (CDOPPP) IN SOWETO, SOUTH AFRICA**

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CDOPPP was established to detect and manage patients with chronic illnesses in the primary health care centers (PHC) at high risk for complications. Managing chronic illnesses is a great challenge. Achieving treatment (Rx) goals and patient follow is difficult. Developing a model for effective management of chronic illnesses remains a challenge.

### **Aims:**

To detect and Rx patients at risk for CVD and CKD, ascertain the programs effectiveness, its ability to facilitate processes of referral and develop clinicians skills.

### **Methods:**

The Wagner Chronic Illness model was used to develop a unique paper based and now computerized model of care, Rx decision support and data analysis. Patients were enrolled at 20 clinics with uncontrolled hypertension (HT); BP  $\geq$ 140/90mmHg; diabetes with HT and/or proteinuria. Other risk factors included cholesterol (mmol/L) and Body Mass Index (BMI kg/m<sup>2</sup>). Standard Rx protocols, patient education, and regular follow up took place. Early referral and failure to follow up were evaluated.

### **Results:**

1425 patients; 60% females, 40% males were enrolled since 2003. 95% had uncontrolled hypertension, 33% had diabetes with HT and/or proteinuria. Advanced disease was common; 9% had stage 3 or > CKD and 0.05% needed immediate dialysis. 12% of patients needed referral for risk factors which could not be managed at the PHC; 56% of these for advanced CKD. Only HT control was significantly improved;  $p < 0.01$  and trends to improvement were evident for the other risk factors ( $p = NS$ ). Poor follow up at many clinics is common the reasons being staff shortages and staff motivation.

### **Conclusions:**

Advanced disease was significant and a common reason for early referral. Risk factors for chronic conditions overlap. Advanced disease remains undetected in the primary care setting, explaining late presentation for care. Early detection, assistance of PHC with management and good follow remain ongoing priorities. Novel ideas like CDOPPP need ongoing support.

VINCENT LAUNAY-VACHER, PHARM D

PARIS, FRANCE

Vincent Launay-Vacher, PharmD  
Paris, FRANCE

The Insuffisance Rénale et Médicaments Anticancéreux (IRMA) study is a French national, observational study. Every cancer patient presenting at one of the 15 oncology departments participating in the study, over at least one of two pre-defined time periods in 2004 were included (only solid tumours, except <18 and ESRD). Renal function was calculated using Cockcroft-Gault (CG) and aMDRD formulae to estimate the prevalence of RI according to the K/DOQI definition. Anticancer drugs were studied with regard to their potential renal toxicity and dosage adjustment.

Of the 4684 patients, 7.2% had serum creatinine levels >110 µmol/L. However, when assessed using CG and aMDRD, 57.4 and 52.9% of patients had abnormal renal function or RI, respectively. Of the 7181 anticancer drug prescriptions, 53.4% required dosage adjustment in RI. Of patients treated, 79.9% received at least one such drug, 80.1% were treated with potentially nephrotoxic drugs.

RI is common in cancer patients, and drug dosage adjustment is often necessary. Renal function should be evaluated in all cancer patients using either the CG or aMDRD formulae, including patients with normal SCR levels. In those patients at high risk for drug toxicity, dosage should be adapted to renal function and the use of nephrotoxic therapies should be avoided whenever possible.

LIZ LIGHTSTONE, MD

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## CKD IN UK ETHNIC COMMUNITIES

Liz Lightstone

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My main interest has been CKD in UK ethnic communities. My original work identified the 3-5 fold increased rates of ESRF in UK Indo Asians compared to Northern Europeans (Lightstone et al, QJM 1995). More recently I had a key role in helping to establish the National Kidney Research Fund's (now Kidney Research UK's) ABLE (A Better Life through Education and Empowerment) campaign designed to raise awareness of and promote research into renal disease in ethnic communities.

My current work is based round multidisciplinary collaborative groups I have established with colleagues in Southampton (Dr Paul Roderick, Medical Epidemiology), Ealing (Professor Jaspal Kooner and Dr John Chambers, Cardiology), South West Thames Renal Research Institute (Dr Marta Lapsley and Dr Mark Dockrell, Clinical Chemistry), Luton (Mr Gurch Randawa, Social sciences), Leicester (Prof John Feehally) and Sheffield (Prof Meguid El-Nahas).

My main research project is a study of cardiovascular and renal risk in a cohort of 30,000 subjects from general practitioner lists in West London – The LOLIPOP study (London Life Sciences Population Study). 70% of the individuals are Indo Asian reflecting the demographics of the local community. Analysis of the first 22,000 subjects demonstrate that the likelihood of having an MDRD eGFR <60mls/min/1.73m<sup>2</sup> is lower in Indian Asian and Black women than their Northern European counterparts and similar among men even when adjusted for age, diabetes, hypertension, vascular disease, metabolic syndrome and smoking. However, Indian Asian and Black men are more likely to have an eGFR of <45mls/min/1.73m<sup>2</sup>. These data, together with the known high rates of ESRF in these ethnic groups, suggest that CKD progresses more rapidly in Indian Asians and Blacks than in Northern Europeans. We also have data on albuminuria, urine retinol binding protein and serum cystatin C from 10,000 of the cohort. We will be reviewing these patients on a 5 year rolling programme to identify incidence of new CKD and the risk factors for progression in the different ethnic groups. We plan to use the LOLIPOP cohort to identify the relationship between CKD and obesity as well as other cardiovascular risk factors. Of note we have stored serum, plasma, DNA and urine which will enable us to identify novel biomarkers associated with progression. Additionally we are looking at attitudes and awareness of CKD in the Indian Asian community and among Indian Asians with diabetes and diabetic nephropathy.

SEIICHI MATSUO, MD

NAGOYA, JAPAN

## **CURRENT STATUS OF NATIONAL MEDICAL POLICIES AND CKD INITIATIVE IN JAPAN**

Seiichi Matsuo<sup>1</sup>, Enyu Imai<sup>2</sup>, Yusuke Tsukamoto<sup>3</sup>, Kunitoshi Iseki<sup>4</sup>

<sup>1</sup>Nagoya University Hospital, <sup>2</sup>Osaka University Hospital, <sup>3</sup>Shuwa General Hospital, <sup>4</sup>Ryukyu University Hospital, Japan

In recent years, Japan has toughened policies to cap on increase in medical expenses. Total medical expense (TME)/GDP is the lowest among G7 countries, and the rate of increase of TME in consideration of aging is the slowest among the developed countries, while the rate of aging is the highest in the world. In 2005, Japan Ministry of Health, Welfare and Labor (MHWL) has launched the New Medical Structure Reconstruction Plan to further lower the increasing rate of TME. The main pillars of the new plan are made of mid-and-long term plans and short-term actions. Among mid-and-long term plans, reduction of lifestyle diseases such as diabetes by 25 % in 10 years is the main objective. Early detection of individuals at risk by compulsory health check paid by health insurance societies, and modification of lifestyle is expected as the first line action. Although it is not yet finally settled, urinary protein/albumin testing is at the increasing risk for being considered as an option rather than essentials in the new compulsory health check system. MHWL explained the reasons for this as follows; (1) proteinuria/albuminuria is not included as a diagnostic criteria for metabolic syndrome in Japan, (2) there is no potent evidence for Japanese by now that early detection of urinary protein in the general population will become a strong driving force to reduce the number of new ESRD patients. Japanese Society of Nephrology (JSN) is now in tough negotiation with MHWL on this important issue, while JSN has been calling for joint action to the related societies and organizations to propagate the importance of CKD. In June 25, 2006, The Japan Association of CKD Initiative (J-CKDI), and has taken action on promoting national CKD campaign in the next year and afterwards.

BOLESLAW RUTKOWSKI, MD

GDAŃSK, POLAND

## **CKD IN POLAND- RESULTS OF THE POLNEF EPIDEMIOLOGICAL PILOT STUDY**

Bolesław Rutkowski, Ewa Król on behalf of the Investigation Team  
Department of Nephrology, Transplantology and Internal Medicine  
Medical University of Gdańsk, Poland

### **Background:**

Continuous increase of the number of patients with chronic kidney failure which require renal replacement therapy, as well in Poland as all over the world, demands the analysis of epidemiological situation concerning renal diseases. Early diagnosis of nephropathy permits not only an adequate treatment, but also facilitates the introduction of the therapy that slows the progression of kidney failure. The aim of the Polish Epidemiological Pilot Study in Nephrology (PolNef) was an attempt to evaluate the epidemiology of kidney diseases in Poland on the basis of a randomly selected population from a city numbering 60 thousand people.

### **Methods:**

As a screening test, allowing distinguishing patients requiring further diagnosis of nephropathy, the microalbuminuria dipstick test accompanied by blood pressure measurement and questionnaire was accepted.

### **Results:**

2475 individuals participated in the pilot PolNef study. Microalbuminuria was detected in more than 16% of the investigated population. It was significantly more frequent in male and in obese. 501 persons were referred to nephrologists. Decreased GFR estimated from serum creatinine (eGFR) was found in about 47% of those participants referred to kidney consultation, and more than 17% of them had eGFR below  $60\text{ml/min/1.73 m}^2$ . 6 persons were referred for further treatment because of newly diagnosed kidney tumor.

### **Conclusions:**

Microalbuminuria occurs frequently in the general Polish population and together with blood pressure measurement and questionnaire seems to be powerful tool to identify subjects at risk for chronic kidney disease. Our results confirmed data from other epidemiological studies performed throughout the world (USA, Australia, Netherlands etc) indicating that unrecognized chronic kidney disease are very common than it was indicated before also in Polish population. Results of PolNef study served as trigger to the wide introduction of the Program of Early Identification of CKD in Poland which hopefully will bring not only medical benefits for every single patient but also substantial economic benefits in future for health care system as well.

RAJIV SARAN, MD

ANN ARBOR, MICHIGAN, USA

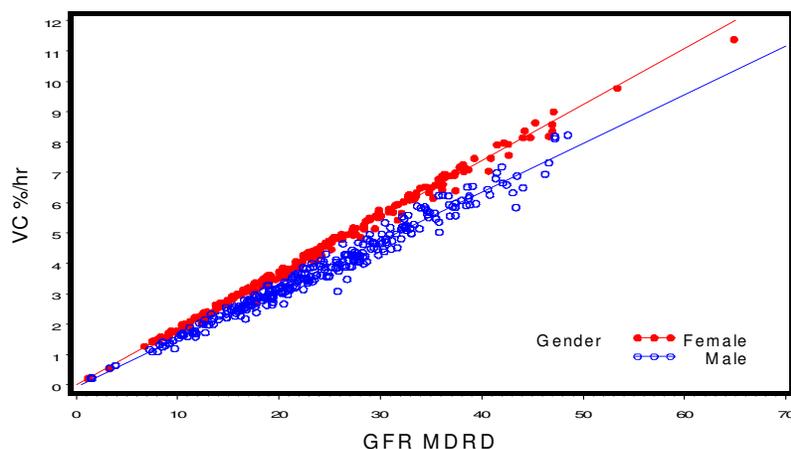
## FRACTIONAL BODY WATER CLEARANCE: A PHYSIOLOGICAL APPROACH TO THE ASSESSMENT OF RENAL FUNCTION: AN ANALYSIS OF THE RRI-CKD STUDY

R. Saran, P.Kotanko, B Gillespie, X Zhang, G. Eisele, M. Kiser, F. Finkelstein, S. Rajagopalan, G. Handelman, F. Gotch, N. Levin

Glomerular filtration rate (GFR) is currently expressed per body surface area (BSA). However, BSA does not reflect the body compartment (Total Body Water; V) cleared by renal function. We therefore compared the approaches of expressing renal function by V and BSA in a cohort of patients with CKD. The RRI-CKD study is a prospective cohort study of stage III-V CKD patients referred to 4 US nephrology clinics. Total body water (V) was estimated using the Watson equation. GFR was estimated by the abbreviated MDRD equation. We additionally calculated renal function as a fraction (percentage) of V cleared per hour (VC%/hr). The mean MDRD-GFR in this cohort of stage III-V CKD was 24.1 ( $\pm$  10.2) ml/min/1.73m<sup>2</sup>. The mean VC%/hour was 3.99 ( $\pm$  0.02), implying that on average, nearly 4% of the total body water was cleared of creatinine per hour. Table below shows a comparison by gender of body size measures, V, GFR and VC%/hour.

Variable	Female Mean $\pm$ Std	Male Mean $\pm$ Std	T-Test P-value
Body Mass Index	29.6 $\pm$ 7.6	29 $\pm$ 6.1	0.36
Body Surface Area	1.8 $\pm$ 0.2	2.1 $\pm$ 0.2	<0.001
Total Body Water (V)	34.3 $\pm$ 5.0	45.7 $\pm$ 7.8	<0.001
GFR (MDRD)	23.7 $\pm$ 10.6	24.3 $\pm$ 9.8	0.42
VC % / hr	4.3% $\pm$ 1.9%	3.7% $\pm$ 1.5%	<0.001

Figure shows the correlation between MDRD-GFR and the VC%/hour by gender.



**Conclusions:** The concept of V cleared per unit time represents a more physiologic approach in considering renal function (similar to Kt/V). At any given MDRD-GFR value, the VC% will be higher for women and those with lower BMI. This approach needs to be tested further for potential clinical relevance.

DAVID SECCOMBE, MD, PHD

VANCOUVER, BRITISH, COLUMBIA CANADA

## **TESTING FOR ALBUMINURIA – TODAY’S REALITY**

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Testing for albuminuria continues to grow with an estimated 100 million tests being conducted annually. The use of this test is being promoted in an ever-expanding set of clinical guidelines for identifying early renal disease, predicting the progression of this disease in diabetes and for monitoring the efficacy of treatment in patients. Integral to these guidelines are “cut offs” or critical test values for albuminuria. Recommendations are being made on the best sample to be tested, the frequency of testing and the clinical decisions that should be considered using this test.

Clinicians frequently assume that laboratory tests have been standardized. Unfortunately, this is not the case. The uniform application of a guideline requires as a pre-requisite standardization of the laboratory tests that it uses. For this purpose, the process of standardization should encompass all aspects of the testing process – pre-analytical, analytical and post-analytical. Standardization is essential to ensure “trueness” of the result over time, to minimize the extent of lab-to-lab variation and to ensure that the test result is communicated with the appropriate reference intervals, interpretative comments and uniform educational messaging from the guideline. Unfortunately, the measurement of albumin in urine has not been standardized. This reality has negatively impacted the discriminating power of this test and has resulted in considerable confusion relating to the measurement, reporting and clinical use of this test. This presentation will examine the testing process for the measurement of albumin in urine within the context of clinical guidelines and standardization.

LESLEY STEVENS, MD

BOSTON, MASSACHUSETTS, USA

## IMPACT OF CREATININE CALIBRATION IN A POOLED STUDY OF INDIVIDUAL PATIENT DATA

Lesley A. Stevens, Jane Manzi, Andrew S. Levey, Jing Chen, Amy E. Deysher, Paul Eggers, Akinlolu Ojo, Emilio Poggio, Michael Steffes, Yaping(Lucy) Zhang, Fred Van Lente, Josef Coresh

Variation in performance of GFR estimating equations is in part, due to differences in creatinine calibration among laboratories. We evaluated the impact of creatinine calibration on performance of the MDRD Study and Cockcroft-Gault (C-G) equations in a pooled dataset consisting of individual patient data from 5504 people in 6 research studies and 2 clinical populations who had GFR measured using urinary clearance of <sup>25</sup>I-iothalamate.

Serum creatinine assays in the individual studies were calibrated to standardized creatinine assay measured on the Roche enzymatic at the Cleveland Clinic using frozen specimens, calibration panel and/or CAP survey results. Linear regression analysis was used to calculate calibration factors. Measurement error was considered by adjustment of coefficients for the R<sup>2</sup> of the regression. Percent bias was calculated as [(measured GFR- estimated GFR)/measured GFR]. C-G was adjusted for body surface area.

For a creatinine value of 1 mg/dl, the median (range) difference between the calibrated and uncalibrated values was -0.12 (0.12). Calibration improved bias, R<sup>2</sup> and P<sub>30</sub> of the MDRD Study equation from 7.9, 0.877 and 80 to 4.4, 0.883 and 83, respectively. Using the C-G equation, the bias, R<sup>2</sup> and P<sub>30</sub> changed from 0.2, 0.843 and 74, respectively, to 7.3, 0.848 and 68, respectively. The table shows the data for the individual studies.

	<b>MDRD</b>				<b>C-G</b>			
	<b><u>Non-Calibrated</u></b>		<b><u>Calibrated</u></b>		<b><u>Non-Calibrated</u></b>		<b><u>Calibrated</u></b>	
	<b>% Bias</b>	<b>/P30</b>	<b>% Bias</b>	<b>/P30</b>	<b>% Bias</b>	<b>/P30</b>	<b>% Bias</b>	<b>/P30</b>
<b>Pooled</b>	5.3	80.4	0.8	83.3	-8.7	74.1	-19.3	68.3
<b>MDRD</b>	-2.3	89.7	-2.1	89.8	-22.4	65.4	-28.8	56.6
<b>AASK</b>	6.0	85.4	0.9	86.6	3.1	75.9	-6.9	74.9
<b>CSG</b>	10.9	75.2	10.0	75.6	-5.6	81.6	-12.3	75.9
<b>CCF</b>	-6.5	71.2	-12.3	69.2	-28.6	59.9	-42.0	48.6
<b>CCF Donor</b>	6.5	86.0	1.4	85.4	-3.7	84.1	-14.5	76.1
<b>DRDS</b>	10.1	76.2	-5.4	81.0	-17.1	69.0	-41.6	49.2
<b>DCCT</b>	12.7	81.1	8.0	84.9	1.4	88.6	-8.9	85.3
<b>MAYO</b>	3.1	76.0	-6.2	76.5	-15.9	68.3	-32.1	54.3
<b>MAYO Donor</b>	27.7	54.0	12.3	87.4	12.9	85.2	-8.7	84.1
<b>CRIC</b>	4.2	81.8	4.9	81.2	-11.5	71.1	-16.9	68.8

Creatinine calibration is critical to accurate MDRDGFR estimates. Use of standardized creatinine may worsen performance of GFR estimating equations that are not re-expressed for use with standardized creatinine assays.

## EVALUATION OF THE MDRD STUDY EQUATION IN A POOLED CREATININE DATASET

Lesley A. Stevens, Josef Coresh, Amy E. Deysher, Paul Eggers, Harold Feldman, James P. Lash, Robert Nelson, Mahboob Rahman, Christopher Schmid, Yaping (Lucy) Zhang, Tom Greene, Andrew S. Levey

Variation in performance of GFR estimating equations amongst individual study populations has been widely reported. We evaluated the MDRD Study equation in a pooled dataset of individual patient data from 5504 people in 6 research studies and 2 clinical populations and described differences in their performance according to individuals' clinical characteristics.

GFR was measured using urinary clearance of  $^{125}\text{I}$ -iothalamate. Serum creatinine was calibrated to standardized creatinine assays at the Cleveland Clinic. GFR was estimated using the four variable MDRD Study equation. Performance was evaluated for the overall group and for subgroups defined age, sex, race, diabetes, transplant, and body mass index (BMI). Analyses were stratified by estimated GFR greater and less than 60 ml/min/1.73 m<sup>2</sup>.

In the overall dataset, median percent bias (IQR) and percent of estimates within 30% of measured GFR (P<sub>30</sub>) was 2.4 (16.4) and 83. GFR estimates greater than 60 ml/min/1.73 m<sup>2</sup> were associated with greater error. Percent bias (IQR) and P<sub>30</sub> were 0.8 (9.4) and 82 for people with GFR < 60, compared to and 6.9 (26.0) and 84, for people with GFR estimates greater than 60. The table shows the results by subgroup.

MDRD Study equation perform better in people with GFR < 60 ml/min/1.73 m<sup>2</sup> and in people similar to those included in the MDRD study. These data may assist in the development of improved estimating equations as well as clinicians' interpretation of GFR estimates as applied to individual patients.

**Table: Percent median bias by subgroup**

		GFR < 60	GFR > 60
<b>Age</b>	< 40	2**	9**
	40-65	4	5
	>65	-2	-2
<b>Female</b>	Y	3	9*
	N	2	6
<b>Black</b>	Y	3	-1**
	N	2	10
<b>Diabetes</b>	Y	5*	10**
	N	2	5
<b>Transplant</b>	Y	-1	-12**
	N	3	8
<b>BMI</b>	< 25	-1**	8
	25-30	4	8
	>30	3	6

\* p-value <0.05; \*\* p-value < 0.001

Age is measured in years; BMI is measured in kg/m<sup>2</sup>

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LuXia Zhang, MD  
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Chronic kidney disease (CKD) has emerged as a public health problem in China. Our works pertain to CKD have been focused on following three issues. The first one relates to the estimation equation of glomerular filtration rate (GFR). MDRD equations provide convenient methods of assessing GFR, while our previous work indicates that when used in Chinese patients, modification of these equations is necessary. So we initiated a multi-center study, and modified MDRD equations based on data of Chinese CKD patients (JASN, 2006, Oct). And we try to improve performance of equations, especially in very early stage of CKD, by combination of cystatin C. Besides, because the calibration of serum creatinine has important effect on the performance of equation, we constructed a model to test the efficacy of two-step calibration of creatinine from practical point of view. The second part of our work is screening for CKD among community-based Chinese population, both in urban and rural area, which revealed urgency of prevention of CKD in China (Chin J Nephrol, 2006, 22: 67-71). And we have just finished a screening work of 16,000 residents, who could represent population older than 18 years in Beijing. Results would be released soon. The last part of our work is about association of CKD with chronic diseases, such as cardiovascular disease (JASN, 2006, 17: 2617-2621), and metabolic syndrome (submitted to JASN), which extend such observation to a population with different genetic and environmental background.