Serum Creatinine Levels, Glomerular Filtration Rate and Renal Insufficiency

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ABSTRACT: Chronic kidney disease (CKD) is a worldwide health problem associated with significant morbidity and mortality requiring dialysis or renal transplant. Serum creatinine and urea levels are raised but estimated Glomerular Filtration Rate (eGFR) is more precise in disease-staging and subsequently referrals for dialysis treatment. Validated equations like Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) are used for eGFR taking into consideration age, sex, ethnicity and serum creatinine levels. In the present study GFR was estimated for 90 CKD patients (average 55.44±1.35y) on hemodialysis treatment but no eGFR documentation. The mean eGFR values were 6.03±0.37 ml/min/1.73m^2 by MDRD and 5.50±0.36 ml/min/1.73m^2 by CKD-EPI equations verifying stage V of CKD in these patients. Both equations performed equally as differences were non-significant though the CKD-EPI equation was more stringent. These observations have significance for staging border-line CKD cases for appropriate treatment strategies and optimizing dialysis therapy.

INTRODUCTION

Renal failure, characterized by the reduction in the excretory and regulatory functions of the kidney, may be acute (in which kidneys revert back to their normal functioning) or chronic where the progressive loss of kidney function becomes permanent or irreversible (Sandoval *et al*., 2012) requiring medical intervention as the only life-saving option. Chronic Kidney Disease (CKD) is a worldwide health, social and an economic catastrophe associated with significant morbidity and mortality (Agarwal *et al*., 2005). In the Indian context, in the absence of nationwide registries due to underdiagnosis and undertreatment of the disease, the exact disease burden of CKD/end stage renal disease (ESRD) cannot be assessed accurately (Agarwal, 2005). However, Agarwal and Srivastava (2009) have documented the prevalence of CKD as 800 per million population (pmp) with an incidence of ESRD between 150-200 pmp.

Increasing frequency of renal failure has been attributed to the increased prevalence of diabetes and hypertension (Agarwal, 2005). Other associated risk factors include obesity, hypercholesterolemia and the metabolic syndrome (Prabahar *et al.*, 2008). Another attribute of CKD is the significantly increased risk of a cardiovascular event (Cheung *et al*.,'04), and of cancer (Rao, 2009).The only mode of treatment/ management for CKD/ESRD is dialysis and/or renal transplant. A study on 1,783,000 renal patients worldwide revealed 77% on dialysis and 23% with a renal transplant, having increased by 7% from the previous year (Grassmann *et al*., 2005). Almost a decade ago in India, there were ~710+ hemodialysis

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units with 2500+ dialysis stations, 172+ transplant centres; of these two-thirds were in South India and mostly private (Keshaviah, 2001). These figures have definitely increased given the frequency of the disease requiring dialysis treatment.

The dialysis process uses a dialysate which flows in the direction opposite to blood flow with its composition adjusted depending on the chronic stage of the disease and the needs of each patient as the type and composition of dialysate impacts dialysis efficiency. Various types of dialysates are used. Of the two dialysates (citrate and acetate), Gabutti (Gabutti *et al*., 2009) observed that the citrate dialysate had higher hemodialysis efficiency compared to the acetate-based dialysate.

The need for dialysis is determined by glomerular filtration rate (GFR) which is considered as an index of functioning renal mass being equivalent to the sum of single nephron glomerular filtration rate and the number of filtering nephrons (Schwartz and Furth, 2007). GFR estimation assists the detection, evaluation and management of CKD. On the basis of GFR values, the disease has been categorized into five stages with the mildest renal insufficiency stages one (GFR $\geq$ 90 ml/minute per 1.73 m^2) and two (GFR between 60-89 ml/minute per 1.73 m^2) and the more severe, third (GFR <60 ml/min/1.73m^2), fourth (GFR <30 ml/min/1.73m^2) and fifth (GFR<15 ml/min/ 1.73m^2) stages concomitant with increased creatinine levels (K/DOQI Guidelines, 2002).

GFR can be measured by renal clearance techniques of inulin clearance or creatinine clearance or can be estimated from serum creatinine and cystatin C levels (Schwartz and Work, 2009). Although inulin clearance method is optimal, yet it is costly and difficult in routine usage as well as impracticable in children. Creatinine, a product of enzymatic degradation of creatine (synthesized in skeletal muscles) is eliminated exclusively via glomerular filtration and shows an inverse relationship with GFR. However, as creatinine levels are influenced by age, race or ethnic group and dietary intake, its measurement for clinical assessment of kidney function is not very appropriate. For these reasons, GFR determination is carried out using various equations such as Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, in which weightage is awarded to influencing variables such as age, sex, ethnicity alongwith the serum creatinine levels (Stevens *et al*., 2006). Besides these, there are other equations with some specifically used in child patients. The Cockcroft-Gault equation however is less accurate in older and obese people compared to the MDRD equation (Froissart *et al*., 2005) while the CKD-EPI equation was observed to be more accurate compared to the MDRD equation (Levey *et al*., 2009).

As the estimated GFR (eGFR) assists in ascertaining the stage of kidney disease and subsequently referrals for dialysis treatment, it is important to have exact eGFR values. For the CKD patients in local hospitals undergoing dialysis, the hospital records had not documented as to if and how GFR estimation was done prior to dialysis though the nephrologists orally discussed that Cockcroft-Gault and MDRD equations were used. Hence it was thought of historic importance to compare the GFR values obtained using the MDRD and CKD-EPI equations for staging of the CKD. As serum creatinine levels are influenced by age, race or ethnic group and dietary intake (Rule *et al*., 2004), in the present study the estimation of GFR (based on serum creatinine levels and using demographic information in MDRD and CKD-EPI equations) of the CKD patients in local hospitals has been carried out. The objectives are two-fold: to compare the GFR values obtained using the validated MDRD and CKD-EPI equations; and based on the results obtained, to characterize the CKD patients into appropriate renal insufficiency stages. The observational outcomes can assist the physicians in modifying the dialysis regimen/schedule.

METHODS

The study was cleared by the Institutional Ethics Committee and voluntary written informed consent was taken from all the participants. Local hospitals with kidney-care facilities (Dr. Virinder Singh's Kidney Clinic and Dialysis Centre, Mokha Hospital and Kidney Care Centre) were visited to contact the respective nephrologists and hospital personnel for identification of chronic kidney disease patients and for gathering information relating to the components of the dialysis process and the dialysers. Of the patients with varying degrees of renal damage either acute or chronic, the CKD patients were interviewed

and information regarding their demographic and disease-specific variables were recorded on a proforma (designed prior to the study). General information pertaining to age, gender, ethnicity was recorded from the patients. Clinical data included information on history of kidney disease, weight, serum creatinine and urea levels and hemodialysis type and regimen. Information related to age, sex, ethnicity and serum creatinine levels were used for estimation of GFR using CKD-EPI & MDRD GFR calculator (*http://www.kidney.org/gfr*) which gives estimated GFR (eGFR) for both MDRD and CKD-EPI equations. Based upon the calculated GFR values, the staging of CKD patients was done as per standard guidelines (K/DOQI Guidelines, 2002). The results are presented as mean ± S.E.M. The Student's t-test was used to find whether GFR values estimated by the two equations in the total group and separately for males and females were significantly different. Pearson's correlation analysis was performed to find if any of the demographic and disease-specific variables affected eGFR values. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS version 16.0 for Windows) and the level of statistical significance was set at $p \leq 0.05$.

RESULTS

The general characteristics of the studied group are presented in Table 1. The CKD patients (n = 90) on dialysis therapy belonged to the age-groups of 21-40y (11.11%), >40-60y (45.55%) and >60y (43.33%). There were more males (71.11%; mean age 54.26 ± 1.54y) than females (28.88%; mean age 58.34 ± 2.68y) with male to female ratio of ~1.7. Based upon the information gathered on ethnic background, majority of the patients (n = 43, 47.77%) were Jat Sikh, followed by Arora Sikhs (n = 18; 20.00%) and the rest belonged to mixed groups.

TABLE 1

General characteristics of renal disease patients

	Characteristics	No. (%)
Age (in years)(Range)	21-40	10 (11.11)
	>40-60	41 (45.55)
	>60-80	39 (43.33)
Gender	Males	64 (71.11)
	Females	26 (28.88)
Weight# (kg)	35-67	41 (45.55)
	68-100	49 (54.44)
Population sub-group	Jat Sikh	43 (47.77)
	Arora Sikh	18 (20.00)
	Hindu	16 (17.77)
	Ramgarhia Sikh	6 (6.66)
	Baniya	1 (1.11)
	Scheduled caste/ Backward class	6 (6.66)

From medical reports

The information gathered regarding disease-specific variables is presented in Table 2. There were 50% of the patients undergoing dialysis once-a-week whereas 21.11% and 28.88% had a dialysis regimen of twice-a-week and once-a-fortnight, respectively.

TABLE 2

Clinical and disease-specific data of renal disease patients

Features	Range/Mean ±S.E.M.		No. (%)
Hemodialysis regimen	Once-a-week		45 (50.00)
	Twice-a-week		19 (21.11)
	Once-a-fortnight		26 (28.88)
Time-on-dialysis (y)	<1		12 (13.33)
	≥ 1		78 (86.66)
Probable etiology of disease	Hypertension		68 (75.55)
	Diabetes		22 (24.44)
Serum Creatinine levels# (mg/dl) Normal range: male (0.8-1.4); female (0.6-1.4)	Male Patients (4.8-21.7)	11.397±0.55	64 (71.11)
	Female Patients (2.1-17.6)	9.696±0.80	26 (28.88)
Urea level # (mg/dl) (Normal range 8.00-20.00)	Male Patients (43.39-228.30)	128.040±5.56	64 (71.11)
	Female Patients (40.28-211.00)	122.400±0.90	26 (28.88)

From medical laboratory reports

In context of the probable etiology of the disease, hypertension accounted for 75.55% of CKD cases whereas diabetic nephropathy was observed to be the cause among 24.44% CKD patients. Majority of the patients (86.66%) had been undergoing dialysis for more than one year (≥ 1-6y; mean 3.07+0.18y) while only 13.33% were on dialysis therapy for less than one year (mean 6.92±0.69 mo). The mean creatinine levels were ten folds higher (mean 11.397+0.55 mg/dl) in male patients compared to the normal range for men (0.8-1.4 mg/dl) and almost nine times higher in females (mean 9.696+0.80 mg/dl) compared to normal range of 0.6-1.4 mg/dl for females; the serum urea levels (mean 126.41±4.72 mg/dl) were also very much higher than the normal (8-20 mg/dl) values (Molitoris, 2007).

Since all the patients had been recommended dialysis therapy, it was thought appropriate to familiarize with the dialysis process and dialysis units. The dialysis units (five) in both the hospitals were from various manufacturing firms and used either cellulose diacetate or TGA diacetate dialysers. The dialyser flux was low or medium depending on the pore-size of the dialyser/membrane being used. An with an average dialysis cycle of 3.5-4.0h duration. The dialysates contained Elite bicarbonate-1011 Parts A and B. Part A had a composition of sodium (79 mmol/l), potassium (2.00 mmol/l), calcium (1.74 mmol/l), magnesium (0.75 mmol/l), chloride (86.60 mmol/l), acetate (4.00 mmol/l); Part B constituted of sodium chloride (221g) and sodium carbonate (626g). Each membrane was re-used two-three times by the patient; dialysis was performed on available machines and with acetate dialysate in bicarbonate hemodialysis was the only dialysate used.

The dialysis process facilitates the removal of excess water and wastes and restores electrolyte balance which is lost due to chronic impairment of kidneys. In haemodialysis, the machine pumps the dialysate as well as the patient's blood through an extracorporeal fluid circuit (outside the body) and the blood is returned to the patient (Misra, 2005). This circuit includes a hemodialyzer (artificial kidney) consisting of a selectively-permeable membrane that allows fluids and waste (uremic toxins) to pass through, while preventing the exchange of blood components and microorganisms, thereby cleaning the blood. The fluid used to clean the blood (dialysate) flows in the opposite direction to the blood on the opposite side of the membrane, while waste and extra fluid removed from the blood ends up in the dialysate by the process of diffusion, ultrafiltration and osmosis (NIDDK, 2006). The reuse of high-flux dialyzers (which are more porous) is recommended (*cf*. NKF, 2005). Informational details about the dialysis components and facilities from where the patients were interviewed are presented in Table 3.

TABLE 3

Facilities and components of dialysis units

Hemodialysis unit	Dialog+ Nixiso Baxter SPS 1550 Fresenius Medical Care Nipro
Dialysis duration	3.5-4h
Dialyzer Flux	Low Medium
Dialyzer/membrane (types)	Baxter High Performance Cellulose Diacetate hollow fiber dialyser (Japan) Nipro FB-130 TGA Diacetate hollow fiber dialyser (Japan) with effective surface area of 1.3m2
Dialysate (Elite bicarbonate) components	Part A- Sodium (79 mmol/l), Potassium (2.00 mmol/l), Calcium (1.74 mmol/l), Magnesium (0.75 mmol/l), Chloride (86.60 mmol/l), Acetate (4.00 mmol/l) Part B- Sodium chloride (221g) and Sodium carbonate (626g)

In Table 4 are presented the estimated GFR values based on the studied equations. The GFR values obtained using MDRD and CKD-EPI equations revealed mean values of 6.03 ± 0.37 ml/min/1.73m^2 and 5.50 ± 0.36 ml/min/1.73m^2, respectively. Although mean GFR values obtained using MDRD equation were higher compared to those from CKD-EPI equation, the Student's t-test revealed that these values were not statistically significant ($p = 0.311$). These observations indicate that both the equations have performed equally well in classifying these CKD patients on the basis of GFR. The eGFR values obtained from both the equations of all the patients, classified the patients as stage V of chronic kidney disease (GFR being <15ml/min/1.73m^2) and requiring dialysis therapy.

TABLE 4

Estimated GFR (eGFR) from MDRD and CKD-EPI equations

Study Equations	Mean eGFR (ml/min/1.73m^2) ±S.E.M.			p-value[#]
	Males	Females	Total	
Modification of Diet in Renal Disease (MDRD)	6.03±0.36	6.03±0.96	6.03±0.37	0.311
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)	5.45±0.34	5.61±0.97	5.50±0.36	

[#]Non-significance of eGFR values obtained from both equations and between genders (Student's t-test, $p \leq 0.05$)

Correlation analysis revealed a positive but non-significant relationship between the eGFR values obtained by study equations and hemodialysis regimen while as expected, there was a significant negative correlation ($p = 0.000$) for serum creatinine levels and eGFR (obtained both with MDRD and CKD-EPI equations) indicating an inverse relationship.

DISCUSSION

CKD is a growing epidemic, thus its characterization based on GFR values and consequent improved therapeutic modalities can reduce risk of associated complications and the co- morbidities of cardiovascular disease, atherosclerosis, cancer and thereby help improve patient outcomes (Nusair *et al*., 2012).

The patient groups of the present study were all Stage V CKD patients (mean age 55.44 ± 1.35y) on different hemodialysis regimens for an average of 3.07 ± 0.18y. In hemodialysis, blood is cleansed-off the accumulated wastes and excess water with the help of the dialyzer and the dialysate (Weinreich *et al*., '06). Citrate dialysate in bicarbonate hemodialysis has been reported to be more efficient especially in those patients with intradialytic hypertension as it decreases peripheral resistance and helps somewhat in the reduction of blood pressure (Gabutti *et al*., 2009). For the dialysis modalities of the patients of the present study, acetate dialysate with bicarbonate is being used.This is important because its use without bicarbonate may cause hypoxemia and hypotensive episodes after dialysis sessions (Hakim *et al*., '85) and hence, can further compromise the health of the CKD patients.

Serum creatinine was almost ten folds higher (mean 11.397+0.55 mg/dl) in male patients and almost nine times higher in females (mean 9.696+0.80 mg/dl) compared to respective normal (0.8-1.4 mg/dl and 0.6-1.4 mg/dl) values (Molitoris, 2007). Such an increase of creatinine results from impaired kidney functioning. The serum urea levels (mean 126.41 ± 4.72 mg/dl) were also higher than the normal (8-20 mg/dl) values (Molitoris, 2007). Elevated urea levels arise from inability of the kidneys to excrete it and hence its accumulation occurs in the blood (Arora, 2010). Urea levels are raised during chronic renal insufficiency, bleeding in the upper gastro-intestinal system, high stress (high fever), dehydration (most common cause) and from consumption of unusually-high protein foods. However all the patients of the present study had the severe fifth stage of CKD and were on hemodialysis therapy and hence the observed increased urea levels are probably because of renal insufficiency.

TABLE 5

Association analysis of eGFR with demographic and disease-specific variables

Variables		eGFR (ml/min/1.73m^2)	
		MDRD equation	CKD-EPI equation
Age	r	-0.158	-0.201
	p	0.137	0.057
Weight	r	-0.169	-0.184
	p	0.111	0.082
Population sub-group	r	0.069	0.072
	p	0.521	0.503
Serum creatinine	r	**-0.800**	**-0.775**
	p	**0.000**	**0.000**
Hemodialysis regimen	r	0.180	0.173
	p	0.090	0.102

Values in bold are significant ($p < 0.001$)

As the determination of GFR by renal clearance techniques is expensive and furthermore, impractical in children, eGFR values are optimal alternatives for staging renal insufficiency and treatment modalities (K/DOQI Guidelines,'02). Using sex, age and serum creatinine levels to estimate GFR, the MDRD and

CKD-EPI equations were used. The MDRD equation results revealed eGFR of 6.03 ± 0.37 ml/min/1.73m^2 and of 5.50 ± 0.36 ml/min/1.73m^2 from CKD-EPI equation- both these values are almost two-three times lower than the GFR value (<15ml/min/1.73m^2) accounted to stage V renal insufficiency. The K/DOQI Guidelines (2002) have also recommended that Cockcroft-Gault and MDRD equations be used for eGFR so that CKD staging may be appropriate. The importance of eGFR cannot be undermined. Any over- or under-estimation of GFR can lead to wrong clinical decisions in chronic kidney disease patients (regarding determination and progression of disease), subsequently resulting in wrong prescription of fluids, solutes and appropriate dose-medications (Schwartz and Work, 2009).

CONCLUSION

The CKD-EPI equation (not being used in local hospitals) can be adapted as it was seen to perform better than MDRD equation though eGFRdifferences were non-significant (p = 0.311). Gender differences were also not statistically significant for MDRD and CKD-EPI equations. In the present study, the performance of the CKD-EPI and MDRD study equations in CKD patients on dialysis treatment have been found comparable given the non-significant differences between the obtained eGFR values. The use of these equations for eGFR can nonetheless be considered important for staging renal insufficiency in border-line cases. As the CKD-EPI equation has provided more stringent eGFR values than the MDRD equation, hence it may prove useful in more precise identification of the CKD stage and especially delineate border-line cases so that there is appropriate prescription of fluids, solutes and dose- medications for dialysis therapy.

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