"PROGNOSTIC VALUE OF RED BLOOD CELL DISTRIBUTION WIDTH IN PATIENTS WITH CHRONIC KIDNEY DISEASE."

By

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Under the guidance of

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Dated: *September 5th, 2016* ***Dr. ARUN VASIREDDY***

LIST OF ABBREVATIONS

CKD	Chronic Kidney Disease
ESRD	End Stage Renal Disease
eGFR	estimated Glomerular Filteration Rate
RDW	Red Cell Distribution Width
SAPS	Simplified Acute Physiology Score
ECOG	Eastern Cooperative Oncology Group
MDRD	Modification of Diet in Renal Disease
CKD-EPI	CKD – Epidemiology Collaberation
RRT	Renal Replacement Therapy
KDIGO	Kidney Disease: Improving Global Outcomes
NICE	National Institute of Health and Clinical Excellence
NKF	National Kidney Foundation
CrCl	Creatinine Clearance
BUN	Blood Urea Nitrogen
BP	Blood Pressure
SNGFR	Single Nephron GFR
ROS	Reactive Oxygen Species
RAAS	Renin-Angiotensin-Aldosterone System
HbA_1C	Glycated Haemoglobin

ABSTRACT

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR). CKD is a worldwide public health problem.

In India, there is a rising incidence of CKD that is likely to pose major problems for both healthcare and the economy in future years. It has been recently estimated that the age-adjusted incidence rate of ESRD to be 229 per million population (pmp), and >100,000 new patients enter renal replacement programs annually. The prevalence of CKD was observed to be 17.2% with ~6% have CKD stage 3 or worse.[1] CKD risk factors were similar to those reported in earlier studies.

Prevention of end stage renal disease (ESRD) by early detection and treatment is an important tool to stop the growing need for renal replacement therapy. Evaluation of hypertensive patients for the presence of CKD is critical as part of preventive care and treatment strategies. As the prevalence of these risk factors associated to CKD is at an alarming rate, no country can afford to overlook the burden of CKD; therefore prevention, early detection, and intervention are the only cost-effective strategies.[8]

Red cell distribution width (RDW) is a quantitative marker of the variability in size of erythrocytes. It is a routine assay of complete blood count tests and does not

require an additional cost. Elevated RDW reflects increased size variations of red blood cells which indicates altered erythrocyte life span or dysfunctional erythrocytes. RDW is usually used for differential diagnosis of anaemia, especially as a marker in iron deficiency anaemia. In addition, RDW has been found as a predictor of mortality in the general population and in several conditions including: acute and chronic heart failure, acute pulmonary embolism, myocardial infarction, peripheral arterial disease, acute renal failure required renal replacement therapy, and kidney transplant recipients.

It has been demonstrated that RDW could be an additive predictor for all-cause mortality in patients with acute renal failure treated with continuous renal replacement therapy. However, there are no sufficient supporting data regarding progression of End Stage Renal Disease with relation to abnormal RDW and among patients with chronic renal failure treated with maintenance dialysis. Therefore, we aimed to investigate whether RDW was associated with progression of CKD and all-cause mortality in CKD patients on maintenance dialysis.

OBJECTIVES AND METHODOLOGY

To define the patients of Chronic Kidney Disease and to follow-up the Patients of CKD for the progression of the disease and to investigate whether Red cell Distribution Width is associated with progression of CKD and all-cause mortality in patients on maintenance dialysis.

This is a prospective longitudinal study conducted at R.L.Jalappa Hospital, Kolar, Karnataka. After obtaining approval from the ethical committee board and taking

informed consent, 192 patients aged 18 years or more diagnosed with CKD of various stages were enrolled in the study. Those whose diagnosis changed during the course of treatment or who later fit into the exclusion criteria were excluded. Patients were divided into two groups according to the change in RDW values: an RDW-Increased group A (n = 155) and an RDW-Decreased group (n = 37). Progression of CKD is estimated by periodic observation of eGFR values during the follow-up and is correlated with the patients performance status score (ECOG).

RESULTS

Patients in the RDW-Increased group had Higher ECOG scores with follow-up in 1 year compared to the RDW-decreased group. There is progression of ECOG performance status scores[graph-13] of patients in both study groups during the 1 year follow-up period. Out of 192 patients observed, all 29 patients who had died during the study had significantly higher RDW-CV values[table-20] and were in raising trend during their follow-up (p= 0.040+).

Patients in both study groups had a decline in eGFR during their follow-up of 1 year depicting the progression of CKD. Predominantly in the RDW-Increased Group A (n=155) the initial time-averaged eGFR was noted as 24.21±15.31 mL/min/1.73 m^2 and the follow-up after 1 year showed significant decline to 14.58±6.47 mL/min/1.73 m^2 respectively. There is no significant difference seen in the eGFR values observed during the follow-up period in both study groups.

CONCLUSION

This study demonstrated that RDW is related to progression of CKD and could be an additive predictor for all-cause mortality in patients on chronic dialysis. Since RDW is a simple, inexpensive, and widely available test, the data may have significant clinical implications for assessing prognosis and choice of treatment in patients with CKD. The prognostic strength of a rising RDW may be greater than other expensive and clinically inaccessible biomarkers. However, prospective, multicenter studies are needed to observe possible other pathophysiological mechanisms of RDW elevation in ESRD patients.

KEYWORDS

CKD, CHRONIC KIDNEY DISEASE, RED CELL DISTRIBUTION WIDTH, END STAGE RENAL DISEASE, PROGNOSIS

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INTRODUCTION

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR). CKD is a worldwide public health problem.

In India, there is a rising incidence of CKD that is likely to pose major problems for both healthcare and the economy in future years. It has been recently estimated that the age-adjusted incidence rate of ESRD to be 229 per million population (pmp), and >100,000 new patients enter renal replacement programs annually. The prevalence of CKD was observed to be 17.2% with ~6% have CKD stage 3 or worse.[1] CKD risk factors were similar to those reported in earlier studies. Early kidney disease is a silent problem, like high blood pressure, and does not have any symptoms. People may have CKD but are not aware of it because they do not feel sick. It is an insidious disease, and patients with hypertension and diabetes, need to be assessed regularly and managed in line with established guidelines.[2,3] The appropriate evaluation and treatment of hypertension is critical in caring for patients with CKD, as uncontrolled blood pressure can lead to faster decline in kidney function and accelerated development of cardiovascular disease, which is the leading cause of death for CKD patients.[2]

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alarming rate, no country can afford to overlook the burden of CKD; therefore prevention, early detection, and intervention are the only cost-effective strategies.[8]

Red cell distribution width (RDW) is a quantitative marker of the variability in size of erythrocytes. It is a routine assay of complete blood count tests and does not require an additional cost. Elevated RDW reflects increased size variations of red blood cells which indicates altered erythrocyte life span or dysfunctional erythrocytes. RDW is usually used for differential diagnosis of anaemia, especially as a marker in iron deficiency anaemia. In addition, RDW has been found as a predictor of mortality in the general population and in several conditions including: acute and chronic heart failure, acute pulmonary embolism, myocardial infarction, peripheral arterial disease, acute renal failure required renal replacement therapy, and kidney transplant recipients.

Several studies have identified red blood cell distribution width (RDW) as a strong and independent predictor of morbidity and mortality in general population, as well in different groups of patients with morbidities such as acute or chronic heart failure, cardiac arrest, pulmonary embolism, acute coronary syndrome, and even community acquired pneumonia. Recent studies investigated pathophysiological mechanisms of negative cardiovascular outcomes in these populations. Authors hypothesized that the size variations of erythrocytes reflected the functional iron status and functions of bone marrow. Furthermore, endothelial dysfunction, microalbuminuria, which is a marker of cardiovascular risk, inflammation, and increased oxidative stress have been suggested as responsible of increased mortality. RDW has been identified as independent short- and long-term prognostic

marker in intensive care unit patients, which significantly improves risk stratification of simplified acute physiology score (SAPS).

Recently, it has been demonstrated that RDW could be an additive predictor for all-cause mortality in patients with acute renal failure treated with continuous renal replacement therapy. However, there are no sufficient supporting data regarding progression of End Stage Renal Disease with relation to abnormal RDW and among patients with chronic renal failure treated with maintenance dialysis. Therefore, we aimed to investigate whether RDW was associated with progression of CKD and all-cause mortality in CKD patients on maintenance dialysis.

OBJECTIVES

To define the patients of Chronic Kidney Disease and to follow-up the Patients of CKD for the progression of the disease and to investigate whether Red cell Distribution Width is associated with progression of CKD and all-cause mortality in patients on maintenance dialysis.

REVIEW OF LITERATURE

Chronic Kidney Disease (CKD) is a worldwide health problem. Comprehensive data on CKD provided by the Third National Health and Nutrition Examination Survey (NHANES III) note that approximately 800,000 Americans have CKD as manifested by a serum creatinine concentration of 2 mg/dL or greater.[1] More than 6.2 million are estimated to have a serum creatinine concentration of 1.5 mg/dL or greater.[2] Data extrapolated from the Framingham study suggest that approximately 20 million people in the United States are at risk for CKD.[3] Unfortunately, from India there is no longitudinal study and limited data on the prevalence of CKD.

In India too, diabetes and hypertension today account for 40–60% cases of CKD. [4] As per recent Indian Council of Medical Research data, prevalence of diabetes in Indian adult population has risen to 7.1%, (varying from 5.8% in Jharkhand to 13.5% in Chandigarh) and in urban population (over the age of 40 years) the prevalence is as high as 28%.[5,6] Likewise the reported prevalence of hypertension in the adult population today is 17% (14.8% from rural and 21.4% from urban belt). A similar prevalence of 17.4% has been reported by Panesar *et al*. (in the age group of 20–59 years) even from slum-resettlement colony of Delhi. [7,8] With rising prevalence of these diseases in India, prevalence of CKD is expected to rise, and obviously this is the key target population to address.

A study was published in a recent issue of the journal from a rural belt of Karnataka. [9] The population had a mean age of 39.88 ± 15.87 years with 3.82% prevalence of diabetes

and 33.62% of hypertension. Authors found 6.3% prevalence of CKD stage 3; which is the highest reported till date by any Indian worker. It is disturbing to note that there is high prevalence of hypertension in a rural setting where over 75% population had normal or low body mass index. It is disturbing to see the rising prevalence of hypertension and CKD in rural belts. Possibly with shifting population the difference between urban and rural areas is getting blurred. Undoubtedly, we need more Indian data to validate these findings.

Such data also raises a suspicion/possibility of an entity like 'CKD of unknown etiology' (CKDu) [10] in this area, like in certain areas of Sri Lanka and Andhra Pradesh. One is not sure of the underlying cause for CKDu, though suspected agents are cadmium, fluoride, arsenic, pesticides, etc. Renal histology in these cases shows chronic tubule-interstitial nephritis. One seriously needs to think about the existence of such entity in this belt.

Modi and Jha [11] reported an age-adjusted incidence of end-stage renal disease (ESRD) as 229/million population. This is more than double of what has been believed (100/million) over a long time. Was the previous data not very exact or the prevalence has actually risen due to increased longevity and life style diseases, is the point for debate? This study however addressed only ESRD.As one can see from published Indian studies, population screened, and criteria used for CKD diagnosis are different by different workers. Agarwal *et al*. [12] studied south Delhi urban population and reported stage 3 prevalence of 0.785%. They used s. creatinine cut off of over 1.8 mg/dl, done on two occasions (approximate 12 weeks apart) as the defining criteria. Study has limitations; (i) CKD diagnosis is not based on glomerular filtration rate (GFR) (ii) patients with proteinuria have

not been included (iii) creatinine cut off is high; hence the reported figure is much lower than reported by other Indian studies.

Singh *et al*. [13] studied urban and semi-urban population of Delhi. They had 31.2% hypertensives and 7.3% diabetics in the screened population. Based on dipstick proteinuria and GFR calculation by modification of diet in renal disease (MDRD) equation they found 4.2% population to be suffering from stage 3 CKD. However, they didn't repeat the proteinuria testing and study didn't address CKD stage 1 and 2.

The rapid growth in both the incidence and prevalence of CKD will result in a huge influx of patients into the ESRD system. In a recently published Screening and Early Evaluation of Kidney Disease study [14] the mean age of the population was 45.22 ± 15.2 years, and any adult could participate in the study. They performed dipstick proteinuria, and GFR calculation was with CKD-EPI equation. They found the prevalence of CKD as 17.2% with stage 1, 2, 3, 4, 5 as 7%, 4.3%, 4.3%, 0.8% and 0.8% respectively. 43.1% of their cohort had hypertension, and 18.8% had diabetes; a figure that is not a true representation of Indian population.

What one gathers from published data from India is that we are no different from US population in the prevalence of CKD. Today life expectancy of an Indian has increased from 41.38 years (in 1960) to 66 years (2013) [15] and prevalence of diabetes and hypertension is steadily rising. Therefore, like in western world prevalence of CKD is expected to rise with the passage of time. Though a minority of CKD patients reach ESRD (0.15–0.20%/year over

next 10–25 years), this population is 10–100 times vulnerable for cardiovascular (CV) events. Therefore, it is important to identify them and have preventive strategy for CV events in place. [16] It is a known fact that over 50% of diabetics and hypertensives are not aware that they are harbouring the disease, therefore if we target the high risk population than only half the patients are likely to be missed; hence some researchers advocate universal screening. [17] But keeping the economics in mind even for developed countries universal screening is not cost-effective, therefore, it may be prudent to have targeted screening for CKD. [18] But whatever policy one follows, there is little doubt about that there is an urgent need to have appropriate social and political strategy for prevention of CKD.

The increase in both CKD and ESRD populations may also overwhelm the ability of nephrologists and other healthcare providers to fully provide interventions that will improve the length and quality of patients' lives. [18]

DEFINING AND STAGING CHRONIC KIDNEY DISEASE

Several terms are used to describe the period of kidney disease that precedes the institution of Renal Replacement Therapy (RRT) such as pre-ESRD, chronic renal insufficiency, chronic renal failure, and chronic renal disease.[19] Unfortunately, none of these terms is particularly accurate and may be confusing to non-nephrology physicians. The term pre-ESRD gives the impression that dialysis is an inevitable outcome of all kidney diseases. The terms renal insufficiency, chronic renal failure, chronic renal disease, and pre-ESRD have negative connotations. These terms also include the word renal, which is not easily understood by patients. For these reasons, chronic kidney disease is chosen as the defining term.

The definition and classification of CKD are based on measurement of GFR, the best overall measure of kidney function.[20] Factors that influence GFR include both structural or functional kidney disease, as well as patient age. In general, the annual decline of GFR with age is approximately 1 mL/min/1.73 m^2 of body surface area, beginning after the patient reaches approximately 20 to 30 years of age. Although a chronic decline in GFR to a level of less than 60 mL/min/1.73 m^2 is evidence of CKD, substantial kidney damage can exist without a decrease in GFR. In this circumstance, kidney damage is defined as a structural or functional abnormality of the kidney that persists for more than 3 months. Manifestations of kidney damage can include pathologic changes or abnormalities revealed by blood, imaging, or urine tests. Using this definition, CKD is present if the GFR is less than 60 mL/min/1.73 m^2. CKD is also present if the GFR is equal to or greater than 60 mL/min/1.73 m^2, if other

evidence of kidney damage also exists. Table 1 provides a classification and staging system based on the level of GFR.

Since the inception of the classification system in 2002, there have been a few modifications. In 2005, the Kidney Disease: Improving Global Outcomes (KDIGO) Work Group recommended adding the suffix "D" for patients with Stage 5 CKD who were on dialysis and the suffix "T" for those with a functioning kidney transplant.[20] Three years later, the United Kingdom National Institute of Health and Clinical Excellence (NICE) group recommended subdividing Stage 3 CKD into 3a (GFR 59 to 45 mL/min/1.73 m^2) and 3b (44 to 30 mL/ min/1.73 m^2) and adding the suffix "p" for those with confounding proteinuria. These modifications were based on the fact that a lower GFR in Stage 3 and the presence of proteinuria had significant implications on clinical outcomes.

This staging system provides a common language for communication between the various healthcare providers. It allows more reliable estimates of the prevalence of earlier stages and of populations at increased risk for CKD. In addition, evaluation of factors associated with a high risk of progression can be recognized. Treatments can be more effectively examined and the development of adverse outcomes in this population is more easily determined.

TABLE-1 Staging System and Action Plan for Chronic Kidney Disease			
STAGE	DESCRIPTION	GFR (mL/min/1.73 m^2)	ACTION*
0	At increased risk of CKD	≥90 with risk factors †	Screening CKD risk reduction
1	Kidney damage with normal or increased GFR ‡	≥90	Diagnosis and treatment Slow progression of CKD Treat comorbidities Cardiovascular disease risk reduction
2	Mild decrease in GFR	60 to 89	Estimate progression
3A	Mild to moderate decrease in GFR	44 to 59	Evaluate and treat complications
3B	Moderate to severe decrease in GFR	30 to 44	Treat complications Initiate discussions about options for possible future need for renal replacement therapy
4	Severe decrease in GFR	15 to 29	Treat complications Prepare for RRT
5	Kidney failure	<15 or dialysis	Renal replacement if uremic or other indications present

*** Includes actions from preceding stages.**
† Risk factors: hypertension, dyslipidaemia, diabetes mellitus, anaemia, systemic lupus erythematosus, and chronic analgesic ingestion.
‡ Kidney damage as manifested by abnormalities noted on renal pathology, blood, urine, or imaging tests.
Source: Adapted from Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) Advisory Board. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Part 4. Definition and classification of stages of chronic kidney disease. Am J Kidney Dis. 2002;39 (suppl 2):S46–S75.

GLOMERULAR FILTRATION RATE AS AN INDEX OF KIDNEY FUNCTION

Serum creatinine concentration is commonly employed as an index of renal function. It is not an accurate measure of GFR, however, and it is especially inaccurate when the serum creatinine concentration is between 1 and 2 mg/dL. This is because creatinine, unlike inulin, is secreted by the renal tubules. As renal function declines, the amount of creatinine secreted by the tubules increases and raises the amount of creatinine in the urine. This acts to falsely increase the creatinine clearance (CrCl), resulting in an overestimation of GFR. Serum creatinine concentration is also influenced by body mass, muscle mass, diet, drugs, and laboratory analytical methods. "Normal" ranges of serum creatinine quoted by laboratories are misleading because they do not take into account the age, race, sex, or body size of the individual.

Inulin clearance is the gold standard test for measuring GFR. Unfortunately, this test is cumbersome, expensive, and not widely available for clinical use. Iothalamate (^{125}I-iothalamate) clearance estimates GFR and is a reasonably accurate substitute for the inulin clearance method. It is also expensive and somewhat cumbersome to perform as a routine clinical test. A 24-hour urine collection for CrCl is the accepted alternative measure of GFR because it is widely available and is familiar to most clinicians. It is often difficult, however, for patients to perform correctly and is less accurate than either inulin or iothalamate clearance. In addition, this test often overestimates GFR in patients with advanced kidney disease.

To simplify measurement of renal function, GFR estimates from prediction equations are often used. These formulas take into account serum creatinine concentration, age, gender, race, and body size, and are better estimates of GFR than serum creatinine concentration alone. The formulas used are sufficiently accurate. The three most widely used are the Cockcroft-Gault, the Modification of Diet in Renal Disease Study (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.[21,22]

The Cockcroft-Gault equation noted below estimates of creatinine clearance (eCrCl):

$$\text{eCrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ for females}$$

Although it provides an adequate estimate of GFR (eGFR), the MDRD equations [21] are more accurate. MDRD equation 7 is the preferred formula but it requires measurement of blood urea nitrogen (BUN) and serum albumin.

The MDRD formula is as follows:

$$\begin{aligned}\text{eGFR} = {} & 170 \times [\text{serum creatinine (mg/dL)}]^{-0.999} \\ & \times [\text{age (years)}]^{-0.176} \times [0.762 \text{ if female}] \\ & \times [1.18 \text{ if African American}] \\ & \times [\text{BUN (mg/dL)}]^{-0.170} \\ & \times [\text{albumin (g/dL)}]^{+0.318}\end{aligned}$$

An abbreviated form of the MDRD equation that does not require BUN or albumin measurement was also developed and is as follows:

$$\begin{aligned} \text{eGFR} = 186 \times &[\text{serum creatinine (mg/dL)}]^{-1.154} \\ &\times [\text{age (years)}]^{-0.203} \times [0.742 \text{ if female}] \\ &\times [1.21 \text{ if African American}] \end{aligned}$$

The abbreviated form is reasonably accurate. The MDRD equation was tested in more than 500 patients with a range of kidney diseases and ethnicities (European Americans and African Americans). GFR values were validated in the sample group using iothalamate (^{125}I) as the gold standard; however, certain patient groups were not well represented in the MDRD study sample. Therefore, clearance measurements are still required in groups who were underrepresented in the MDRD sample to fully validate the formula for all patients. These include patients at extremes of age and body size; the severely malnourished or obese; patients with skeletal muscle diseases, paraplegia or quadriplegia; vegetarians; and those with rapidly changing kidney function. The MDRD equation underestimates GFR in patients with relatively normal kidney function.

In 2009, the CKD-EPI[22] was developed in an attempt to improve the accuracy of estimating equations in a more heterogeneous group of patients. This formula utilized the same 4 variables as the MDRD equation. Compared with the MDRD equation, the CKD-EPI equation has less bias, particularly at GFR greater than 60 mL/min/1.73 m^2, as well as improved overall accuracy. It also allows reporting of numeric values across the range of GFR measurements.

The CKD-EPI equation is as follows:

$$\begin{aligned} \text{eGFR} = 141 &\times \min(\text{serum creatinine}/k, 1)^{a} \\ &\times \max(\text{serum creatinine}/k, 1)^{-1.209} \\ &\times 0.993^{\text{age}} \; [\times 1.018 \text{ if female}] \\ &[\times 1.159 \text{ if black}] \end{aligned}$$

[k is 0.7 for females and 0.9 for males, a is −0.329 for females and −0.411 for males.]

In the absence of specific modifications for race, ethnicity or regional difference, the CKD-EPI equation is fairly accurate for GFR estimation. To account for possible differences in muscle mass and diet, race, ethnicity and other geographic variables, the MDRD Study and CKDEPI equations have been modified for use in China and Japan. The modifications are associated with improved accuracy in these populations.

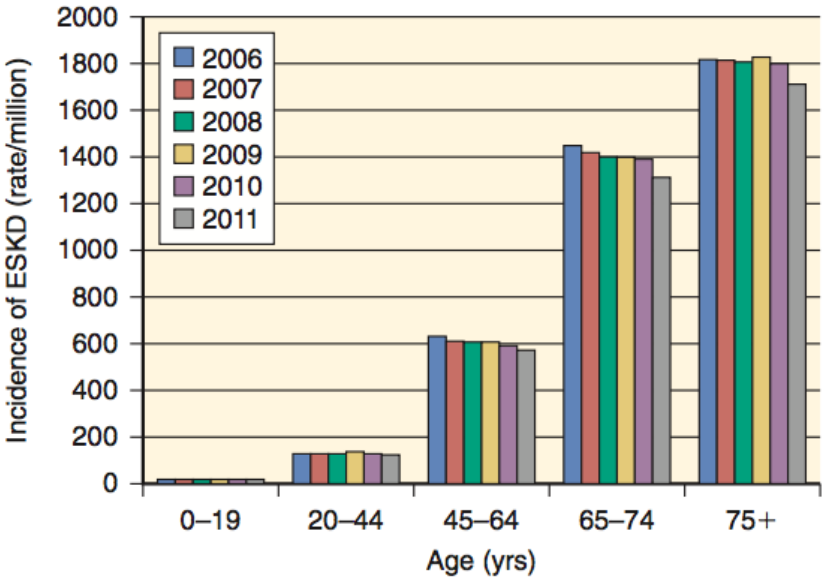
It has been proposed that utilizing both serum creatinine concentration and serum cystatin C together may improve the accuracy of GFR estimation, as compared to either marker alone. This may be particularly useful in patients with CKD 3A (45 to 59 mL/min/1.73 m^2) who do not manifest any markers of kidney damage. Cystatin C may potentially offer some advantages over measurement of serum creatinine concentration in the estimation of GFR and for the proper classification of CKD. Its use, however, is limited by higher cost and "lack of standardization" among the limited number of laboratories that offer the test.

PREVALENCE OF CHRONIC KIDNEY DISEASE STAGES

Prevalence estimates for each CKD stage were obtained by using a reference group comprised of patients evaluated in the NHANES III. In this sample of patients, the MDRD equation was used to estimate GFR. In addition to abnormal GFR levels, the presence of micro- or macro-albuminuria on spot urine specimens was considered sufficient evidence of kidney damage. The level of albuminuria, based on the ratio of albumin (and protein) to creatinine on spot urine samples, was used to estimate the prevalence of the first 2 stages.

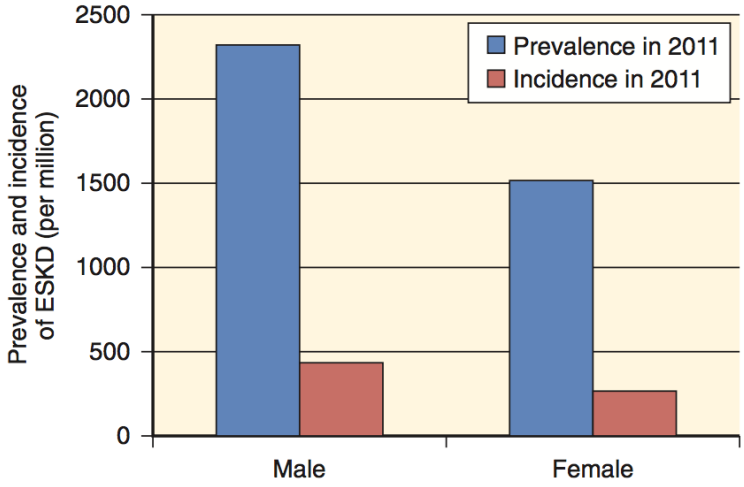
The reported prevalence of CKD Stages 1 to 4 in the most recent NHANES between 1999 and 2006 was 26 million (13%) out of approximately 200 million United States residents 20 years of age or older. Approximately 65% had CKD Stage 3 or 4. The USRDS estimates that nearly one-half million U.S. patients were treated for ESRD in the year 2004, and by 2010 this figure increased by approximately 40%.

The elderly are a growing segment of the population and are clearly at increased risk for kidney disease. Males and African Americans with pre-existing hypertension or diabetes mellitus and CKD are also at higher risk for development of ESRD.



GRAPH 1 - : Incidence of ESRD with age

(Adapted from *USRDS 2010 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*, Bethesda, MD, 2010, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.)[19]



GRAPH 2 - : Prevalence and Incidence of ESRD according to gender

(Adapted from *USRDS 2010 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*, Bethesda, MD, 2010, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.)

APPROACH TO CHRONIC KIDNEY DISEASE PATIENTS

The approach to the patient involves establishing the presence of CKD, determining the stage of disease, and enacting an action plan based on the stage. The management of CKD patients requires a multidisciplinary approach involving primary care physicians, nephrologists, endocrinologists, cardiologists, vascular surgeons, physician assistants, nurse practitioners, dietitians, and social workers. The goals of this interdisciplinary approach are to identify patients either with or at increased risk for CKD, to slow the progression of CKD to ESRD, to identify and treat comorbid conditions, to identify and prevent complications of CKD, and to prepare patients mentally and physically for RRT.

Patients with established CKD are assessed for comorbid conditions. Medications are adjusted for the level of renal function. Blood pressure (BP) monitoring is essential to diagnose hypertension and facilitate optimal BP control.[23] Serum creatinine concentration is measured to allow estimation of GFR. Protein- or albumin-to-creatinine ratios on spot urine samples and urinalysis are performed. Finally, imaging of the kidney by ultrasound is warranted in most CKD patients.

The approach is implemented in a stepwise fashion and individualized for each patient based on the level of kidney function. In a patient with a normal GFR (≥90 mL/min/1.73 m^2) or a mildly impaired GFR (>60 mL/min/1.73 m^2) the focus will be on delaying progression

and treating comorbid conditions. Progression is best predicted by plotting the reciprocal of the serum creatinine concentration over time. This plot predicts a date when the GFR will reach target levels and can be used along with symptoms and signs for deciding the appropriate time for initiation of RRT.[24]

TABLE 2 - LEADING CATEGORIES OF ETIOLOGIES OF CKD
Diabetic nephropathy
Glomerulonephritis
Hypertension-associated CKD (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension)
Autosomal dominant polycystic kidney disease
Other cystic and tubulointerstitial nephropathy

MECHANISMS OF PROGRESSION OF CHRONIC KIDNEY DISEASE

Much of what we understand about the mechanisms involved in the progression of CKD has been obtained through "experimental kidney disease." Progression of CKD may be considered as a process of "glomerular adaptation." In experimental models, adaptation is characterized by an increased workload per nephron, and this is manifested as increased "single nephron GFR (SNGFR)." [24] The increase in SNGFR is initially "adaptive," but eventually becomes "maladaptive," because it leads to further nephron injury. There are several theories that have been suggested to account for this:

1. Hemodynamic hypothesis
2. Abnormal permeability to macromolecules
3. Growth Factor Hypothesis

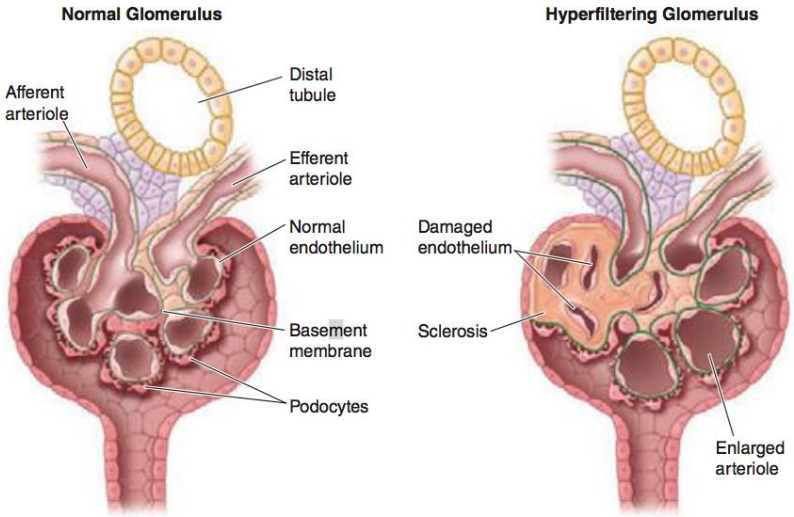


Figure - 1 : Secondary glomerular changes associated with a reduction in nephron number, including enlargement of capillary lumens and focal adhesions, which are thought to occur consequent to compensatory hyperfiltration and hypertrophy in the remaining nephrons. *(Image courtesy from JR Ingelfinger: N Engl J Med 348:99, 2003.)*

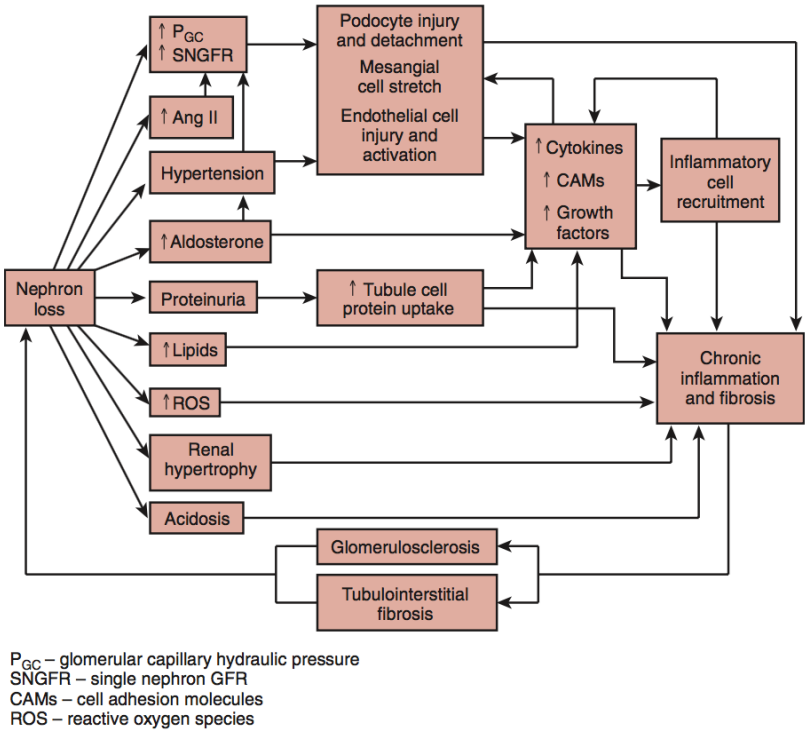
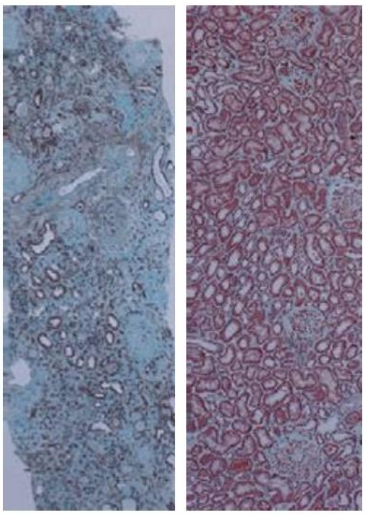


FIGURE 2 - Schema illustrating the hypothesized interaction of multiple hemodynamic and non-hemodynamic factors in the pathogenesis of progressive nephron injury in chronic kidney disease. Ang II, Angiotensin II. (image courtesy: Brenner and Recter's The Kidney 10th edition)

HEMODYNAMIC HYPOTHESIS

In experimental settings, ablation of kidney mass is achieved through a unilateral nephrectomy followed by ligation of the renal artery branches in the remaining functioning kidney, thereby causing an infarction of approximately two-thirds of said kidney. By reducing the number of nephrons to one-sixth, GFR reduction ensues. Following a reduction in the number of functioning nephrons, the remaining nephrons experience hyperfiltration and glomerular capillary hypertension. Although these changes are initially adaptive to maintain GFR, over time they are deleterious to renal function because of pressure-induced capillary stretch and glomerular injury. Histopathologically, this progression of events is manifested as glomerular and tubular hypertrophy followed by eventual focal glomerular sclerosis, tubular atrophy, and interstitial fibrosis. Damage caused by glomerular hyperfiltration is notably important in the pathophysiology that underlies diabetic nephropathy.

Another experimental kidney disease model mimicking diabetes mellitus utilizes alloxan or streptozotocin to chemically ablate pancreatic islet cells. The hyperfiltering state induced by hyperglycemia upregulates local expression of the renin-angiotensin-aldosterone system (RAAS) and contributes to progressive kidney damage. In this instance, stimulation of the RAAS causes glomerular injury by further raising glomerular capillary pressure through angiotensin II (AII)-driven efferent arteriolar vasoconstriction and facilitating pressure and stretch injury in the capillaries. Taken together, these effects lead to endothelial injury, stimulation of profibrotic cytokines by the mesangium, and detachment of glomerular epithelial cells.[25]



Left: Low-power photomicrograph of a normal kidney showing normal glomeruli and healthy tubulointerstitium without fibrosis.

Right: Low-power photomicrograph of chronic kidney disease with sclerosis of many glomeruli and severe tubulointerstitial fibrosis

(Masson trichrome 40x magnification). *(Slides courtesy of the late Dr. Andrew Herzenberg*.)

ABNORMAL PERMEABILITY TO MACROMOLECULES

Another consequence of renal injury and activation of the RAAS is proteinuria. Glomerular capillary hypertension, caused by hyperfiltration and AII effect on efferent arterioles, leads to an increase in glomerular permeability and excessive protein filtration. Pore size is altered by AII, increasing protein leak across the glomerular basement membrane. An activated RAAS may also cause proteinuria through novel effects on nephrin expression in kidney. Nephrin, a transmembrane protein located in the slit diaphragm of the glomerular podocyte, is thought to play a key role in the function of the glomerular filtration barrier. By maintaining slit diaphragm integrity, nephrin limits protein loss across the glomerular basement membrane. When its expression is disrupted, proteinuria and its consequences may result. Data in rat models of proteinuric kidney disease suggest an important interaction between the RAAS and nephrin in modifying glomerular protein permeability.

Although proteinuria is a marker for renal disease risk, it is also likely that excess protein in urine contributes to progressive kidney damage. Proteins present in the urine are toxic to the tubules, and can result in tubular injury, tubulointerstitial inflammation, and scarring. Tubular damage is caused by protein overloading of intracellular lysosomes, stimulation of inflammatory cytokine expression, and extracellular matrix protein production. These processes induce renal tubulointerstitial fibrosis and glomerular scarring. Remission or reduction in proteinuria is often associated with renoprotection and slowed progression of kidney disease.

GROWTH FACTOR HYPOTHESIS

Although it is known that elevated glomerular capillary pressure and capillary stretch lead to scar formation in the glomerulus, an activated RAAS and other inflammatory mediators cause irreversible damage in the kidney through other mechanisms. Pro-inflammatory and profibrotic effects of AII and aldosterone underlie the injury that develops in the renal parenchyma.

Advanced glycation end-products (AGEs) accumulate in the mesangial area and glomerular capillary walls in diabetic nephropathy patients, and as such may have a role in perpetuating renal injury.[23] AGEs are a heterogeneous group of compounds that are produced by non-enzymatic, sequential glycation and oxidation reactions of sugars with free amino groups on proteins, peptides, or amino acids. There are several pathways by which AGEs cause renal injury:

- AGEs interfere with extracellular matrix proteins (collagen, elastin, and laminin) leading to alterations in both structure (induces fibrosis) and function (hydrophobicity, charge, elasticity, and turnover).

- AGE–RAGE interactions. AGE may also produce cellular injury by a cascade of receptor-dependent (RAGE) events that leads to transformation of tubular cells into myofibroblasts, leading to development of tubular atrophy and interstitial fibrosis.

- AGEs are also involved in receptor-independent interactions that lead to intracellular generation of reactive oxygen species (ROS). ROS activate signaling pathways (eg, mitogen-activated protein kinases, protein kinase C, Janus kinase/signal transducers and activators of transcription), which lead to pro-inflammatory (eg, nuclear factor kappa B [NF- κB], monocyte chemoattractant protein-1, tumor necrosis factor [TNF]- α) and profibrotic (eg, transforming growth factor [TGF]- β , connective tissue growth factor, platelet-derived growth factor [PDGF]) effects.

- Accumulation of AGEs also leads to endothelial dysfunction (indirectly), increased thrombogenicity and accelerated atherosclerotic changes, and subsequent end-organ hypoperfusion.

Another maladaptive consequence is increased ammoniagenesis per remnant nephron. This effect promotes complement cascade activation and enhanced injury to the tubulointerstitium. These effects are thought to be related to the actions of excess aldosterone

and endothelin-1 stimulated by impaired elimination of the daily acid load and subsequent acid retention (inherent in CKD). This concept has led to the notion that dietary alkali therapy may have a potential role in preserving GFR and delaying progression of CKD.[24]

These various mediators promote fibrosis and scarring in the kidney through multiple untoward effects such as toxic radical formation, enhanced cellular proliferation, and collagen deposition in the glomerulus and tubulointerstitium. Ultimately, glomerulosclerosis and tubulointerstitial fibrosis occur and promote CKD.

RISK FACTORS FOR PROGRESSION OF CKD

The risk factors for CKD progression can be classified into

1. Susceptibility factors - these are the factors that predispose to CKD. These include genetic and familial predispositions, race, maternal-fetal factors, age, and gender.

2. Initiation factors - These are the factors that precipitate injury to the kidneys.

    i. Systemic hypertension
    ii. Diabetes mellitus
    iii. Cardiovascular disease
    iv. Obesity/metabolic syndrome
    v. Hyperuricemia

vi. Smoking
vii. Low socioeconomic status
viii. Nephrotoxins (NSAIDs, analgesics, herbal supplements, heavy metals, etc)

3. Progression factors - These are the factors associated with progression of damage to established kidney disease.
    i. Older age
    ii. Male gender
    iii. Race/ethnicity
    iv. Genetic predisposition
    v. Poor blood pressure control
    vi. Poor glucose control Proteinuria
    vii. Cardiovascular disease
    viii. Dyslipidemia,
    ix. smoking,
    x. obesity/metabolic syndrome,
    xi. hyperuricemia,
    xii. low socioeconomic status
    xiii. ETOH consumption,
    xiv. nephrotoxins (NSAIDs, analgesics, herbal supplements, contrast material, etc)
    xv. Acute kidney injury

These factors are further classified as either modifiable or nonmodifiable, based on feasibility for intervention.[27]

MODFIABLE RISK FACTORS FOR PROGRESSION.

1. Hypertension and the RAAS
2. Diabetes Mellitus
3. Dietary Protein
4. Hyperlipidaemia
5. Dietary Salt
6. Hyperuricemia
7. Obesity
8. Smoking

HYPERTENSION and The RAAS

Hypertension is clearly associated with progression of CKD and is the second most common cause of ESRD. Importantly, hypertension is present in the majority of CKD patients, making it a key risk factor for progression. Most studies, with a few exceptions confirm that hypertension hastens the course of CKD to ESRD in both diabetic and nondiabetic patients. The MDRD study demonstrated that proteinuric patients, when randomized to a lower BP, manifested a slower decline in GFR. Also, significant correlation between the achieved BP and the rate of renal function decline, especially in patients with greater than 1 g/day of proteinuria, was noted.

The Joint National Committee[23] (JNC VII) recommends the following BP target goals:

1. CKD with less than 1 g/day of proteinuria: 130/80 mmHg.
2. CKD with more than 1 g/day of proteinuria: 125/75 mmHg.

Since the JNC VII Guidelines were published in 2003, several studies have questioned the recommendation of targeting a BP of 130/80 mmHg in CKD patients without albuminuria. Studies suggest that data from the general population are not necessarily applicable to the CKD population. Furthermore, some suggest that tight BP control may have adverse consequences particularly in the elderly and those with coronary artery disease. Several randomized controlled trials (RCTs) failed to demonstrate a significant benefit of aggressive lowering of in those without proteinuria. The AASK (African American Study of Kidney Disease and Hypertension) found there was notable benefit in targeting a lower BP (mean arterial pressure [MAP] ≤92 mmHg) for those with urine protein-to-creatinine ratio greater than 220 mg/g, whereas, no benefit was seen in those with urine protein to creatinine ratio less than 220 mg/g. A similar finding was demonstrated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD)[28] trial, whereby a target systolic BP less than 120 mmHg was not significantly beneficial, as opposed to a target systolic BP less than 140 mmHg. Analysis of the effect of BP control on progression to ESRD was assessed in 16,128 CKD patients in the Kidney Early Evaluation Program (KEEP).[14] In this large, diverse population, progression to ESRD started at a systolic BP of 140 mmHg rather than the recommended goal of 130 mmHg. Progression was highest in those with a systolic BP at least 150 mmHg. Thus, we may need to change target BP for CKD patients.

Proteinuria is a powerful risk factor for progression of CKD, especially as levels exceed both 1 and 3 g/day, respectively. Patients with high-grade proteinuria and hypertension are at highest risk to progress to ESRD. MDRD Study A data demonstrated significant benefit in kidney outcomes in patients with proteinuria greater than 1 g/day, particularly in those with GFR between 25 and 55 mL/min/1.73 m 2 and a trend toward benefit in patients with lower levels of proteinuria. This was supported by the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) study, which also showed that a low BP target was beneficial in decreasing the risk of kidney outcomes in those with higher urine protein levels.[29]

Both experimental and clinical data suggest that inhibition of the RAAS is very effective in lowering BP, reducing proteinuria, and slowing progression of kidney disease in both diabetic and nondiabetic patients. This is of particular interest as the leading cause of ESRD in the United States is diabetic nephropathy. Treatment of disease states resulting from or associated with excessive RAAS activity is best achieved by therapies that suppress AII and aldosterone production or inhibit the renal effects of these substances.

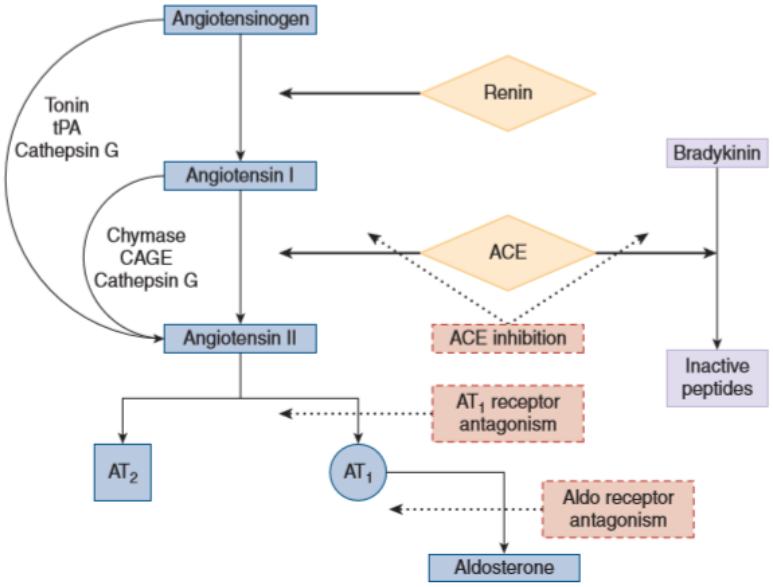


FIGURE 3 - The RAAS. AII and aldosterone are formed by classical pathways (renin, angiotensin-converting enzyme [ACE]) and alternate pathways (tonin, tPA, cathepsin G, chymase, CAGE). The pathway is interrupted at various levels by ACE inhibitors, AT 1 receptor antagonists, and aldosterone receptor antagonists. Abbreviations: A T 1 , angiotensin type 1; AT 2 , angiotensin type 2; CAGE , chymostatin-sensitive angiotensin II-generating enzyme; t PA , tissue plasminogen activator. (Courtesy of Mark A. Perazella.)

The choice between ACE inhibitors and ARBs in CKD, however, is an area of controversy. In general, the evidence for ACE inhibitors and improved kidney outcomes are older and mostly apply to type 1 diabetics. On the other hand, evidence for the use of ARBs in type 2 diabetics is contemporary. Data on cardiovascular protection in diabetic patients are noted with ACE inhibitors. Current evidence suggests that the effects of both agents are likely similar. A recent metaanalysis noted that there was insufficient evidence on the relative effects on survival when comparing both classes. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Randomized Assessment Trial (ONTARGET), which

enrolled people with high cardiovascular risk (including those with diabetes and CKD), did not show a clear difference between the 2 classes of drugs. This study, however, was believed to be relatively underpowered for this comparison.[30]

Previously, dual blockade of the RAAS with ACE inhibitors and angiotensin receptor blockers was considered to provide kidney benefit beyond therapy with either drug alone. One notable study that supported this notion was the Candesartan and Lisinopril Microalbuminuria (CALM) study.[31] This study combined lisinopril and candesartan to treat hypertension and reduce microalbuminuria in patients with type 2 diabetes mellitus. Over 24 weeks, dual blockade safely reduced BP and reduced microalbuminuria (50%) as compared with candesartan (24%) and lisinopril (39%) monotherapy. Similarly, a randomized double-blind crossover study in 18 type 2 diabetic patients with proteinuria demonstrated positive renal effects with combination therapy. In patients with immunoglobulin (Ig) A nephropathy, the combination of losartan and enalapril were additive in decreasing urinary protein excretion, whereas doubling the dose of either form of monotherapy had no effect on proteinuria. Over 6 months, the combination of lisinopril plus candesartan reduced proteinuria by 70% compared to monotherapy with lisinopril (50% reduction) or candesartan (48% reduction). Not all studies demonstrate that combination therapy is better than maximal dose ACE-inhibitor therapy in decreasing proteinuria. These studies suffer from small patient numbers, surrogate markers of renal protection (proteinuria), and short-term follow-up.

In a recent trial, combination RAAS blockade therapy was associated with an increase in adverse events, especially impaired kidney function and hyperkalaemia, as compared with either agent alone. This occurred despite significant albuminuria reduction with combination therapy. In ONTARGET, combination therapy failed to improve cardiovascular end points despite additional BP reduction averaging systolic blood pressure 2.4 mmHg/diastolic blood pressure 1.4 mmHg.[30] At the present time, dual RAAS blockade with an ACE inhibitor and an ARB is not recommended, a recommendation supported by the American Society of Hypertension's Position Article on combination therapies. Thus, titration of the single agent to maximal dose to control BP and proteinuria is recommended. If proteinuria remains greater than 1 g/day, a second agent to further block the RAAS is not recommended but may be useful in certain individuals. The risks and benefits of this therapy must be carefully weighed.

Aldosterone, the last hormone in the RAAS pathway is associated with renal injury through both hemodynamic and profibrotic effects. Aldosterone antagonism in animals is renoprotective when used alone or in combination with ACE inhibition. Preliminary human data suggest that the combination of an aldosterone receptor antagonist like spironolactone or eplerenone with an ACE inhibitor or ARB significantly reduce proteinuria. This therapy, however, is associated with higher risk of hyperkalaemia.

Finally, it is important to recognize that with close patient monitoring, RAAS inhibitors can be used safely in most patients with mild-to-moderate CKD. The 2 major concerns associated with these drugs are the development of hyperkalaemia

and/or further worsening of kidney function. In regards to hyperkalaemia, careful dose titration, dietary changes, avoidance of potassium-altering medications (nonsteroidal anti-inflammatory drugs [NSAIDs], cyclooxygenase [COX]-2 selective inhibitors, potassium-sparing diuretics, etc), and use of loop diuretics allow safe therapy in most patients. Increases in serum creatinine concentration should be tolerated as long as the concentration rises no higher than 30% above baseline and stabilizes within 2 months of therapy.[32] Continued increases should promote drug discontinuation and a search for volume contraction, critical renal artery stenosis, and other potentially correctable problems.

DIABETES MELLITUS and CKD

As the prevalence of diabetes mellitus grows in India, patients with this disease continue to contribute a significant number of patients to the CKD population. In fact, diabetic kidney disease is the most common cause of ESRD. Thus, it is important to identify and adequately manage these patients to reduce progression of their underlying kidney disease. As shown in the Diabetes Control and Complications Trial (DCCT), intensive insulin therapy to establish tight glucose control prevented de novo kidney disease (microalbuminuria) by 34% and reduced progression of established nephropathy (albuminuria) by 56% in type 1 diabetics. Progression of CKD in type 2 diabetics is an even bigger problem as this group makes up the majority of patients who develop ESRD. Earlier studies revealed that intensive insulin therapy to maintain the glycosylated haemoglobin (HbA1c) level in the 7.0% to 7.6%

range reduces progression of kidney disease (albuminuria/proteinuria) as compared with conventional insulin therapy.[19]

Several trials conducted in diabetic patients to determine whether or not early and/or more intensive glycaemic therapy might further decrease the frequency of CKD and ESRD. Aggressive glycaemic control did not translate into better outcomes, and in certain situations, were harmful. Based on these trials, recommendations have been modified to target HbA1c approximately 7% to prevent or delay microvascular complications including overt diabetic nephropathy. Thus it appears that in diabetics with higher CKD stages, either high (>8% to 9%) or low (<7%) HbA1c levels are harmful in regards to mortality, progression of kidney disease and other clinical endpoints.[26]

As HbA1c may not be truly accurate (falsely low as a result of decreased red blood cell [RBC] lifespan, transfusions, and haemolysis) in CKD patients, studies must adjust for this finding or develop another assay for these patients. To address this issue, research efforts are focused on glycated albumin as a measure of diabetic control in those with advanced stages of CKD.

DIETARY PROTEIN

Restriction of dietary protein reduces renal injury in the experimental setting by decreasing glomerular capillary hypertension and reducing production of profibrotic cytokines and growth factors. In humans, it is less clear that a low-protein diet is beneficial. The results of various studies are mixed. In the largest study, 2 levels of protein restriction (low and very low) failed to show a difference in GFR decline between groups after a mean follow-up of 2.2 years. Post hoc analysis identified some benefit of protein restriction when examined by achieved level of protein intake. Patients with the very low protein intake had a 1.15 mL/min/year slower decline in GFR. Two meta-analyses also suggest a benefit with protein restriction. In one, the risk of ESRD or death was reduced by 33% while another noted a small benefit in GFR change (0.53 mL/min/year) with a low-protein diet.[33] Enthusiasm for this approach is tempered by the real risk of malnutrition in CKD patients.

Protein diets above the recommended daily intake may increase the rate of progression of kidney disease particularly in those with earlier stages of CKD. In the Nurses Health Study, the effect of protein intake over 11 years in 1624 enrolled females, divided into those with baseline GFR greater than 80 mL/min/1.73 m 2 (normal kidney function) and those with baseline GFR 55 to 80 mL/min/1.73 m 2 , was examined. In those with normal baseline kidney function, there was no significant association between high protein intake and change in eGFR. However, in the latter group, protein intake was associated with a significant decrease in eGFR of approximately 1.69 mL/min/1.73 m^2 per 10-g increase in protein intake. This effect was most significant in those who consumed a diet consisting of high non-dairy animal-protein content.

Current evidence supports no benefit to dietary protein restriction of less than 0.8 g/kg/day.[33] However, high total protein intake (>1.3 g/kg/day), especially high non-dairy animal-protein content, may increase the rate of GFR decline in CKD patients, and is therefore not recommended.

HYPERLIPIDAEMIA

Experimental work demonstrates that low-density lipoprotein (LDL) lipids are toxic to human mesangial cells, an effect that is reversed by 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors (statins). Observational studies in humans suggest that reducing serum lipid levels is associated with preservation of kidney function.[25] Unfortunately, these studies are plagued by small patient numbers and as a result, are underpowered for drawing any conclusions. To address this problem, a meta-analysis of 13 studies revealed a trend toward reduction in proteinuria and a small decrease rate of GFR loss with lipid lowering.

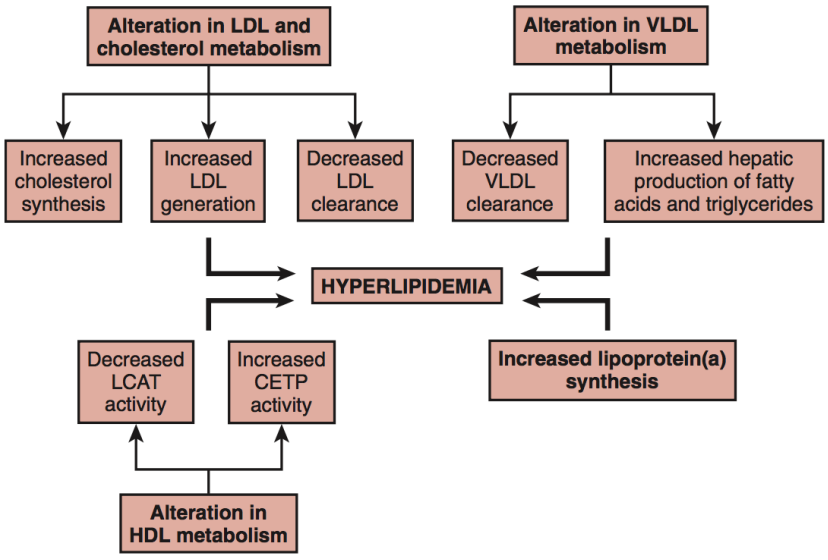


Figure - 4 : Pathophysiology of nephrotic hyperlipidemia. All abnormalities of lipid pro le originate from alterations in low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), high-density lipoprotein (HDL), and cholesterol metabolism as well as increased synthesis of lipoprotein(a). CETP, cholesterol ester transfer protein; LCAT, lecithin-cholesterol acyl transferase.

Two large scale RCTs (Prevention of Renal and Vascular End-stage Disease Intervention Trial [PREVEND-IT] and European Study for Preventing by Lipid-lowering Agents and ACE-inhibition Dialysis Endpoints (ESPLANADE) failed to show a beneficial effect of statins on albuminuria in patients who were treated with ARBs. The SHARP (Study of Heart and Renal Protection) study, a randomized, prospective, controlled trial examining the combination of ezetimibe and simvastatin, showed that all-cause and cardiovascular mortality were not improved. Combination therapy did not decrease the risk of progression to ESRD in CKD patients who were not on dialysis at baseline, as compared with placebo. The primary mortality benefit of therapy was limited to patients with hyperlipidemia, particularly CKD Stages 3 and 4 (but not in CKD Stage 5 or those on dialysis). Based on the results of SHARP, it appears that statin therapy does have a role— perhaps at least a statin combined with ezetimibe—in patients with CKD Stages 3 to 4. A major limitation is high cost.

DIETARY SALT

CKD patients are at risk to develop salt and water overload as a consequence of reduced GFR, upregulated neurohormones, and other disturbed physiology. A direct correlation between a high sodium diet and increased arterial pressure, proteinuria, and decreased in GFR are well described.

A low-sodium diet may significantly reduce proteinuria and arterial pressure as shown in a crossover RCT where the addition of a low sodium diet to ACE inhibitor therapy significantly reduced proteinuria as compared with the addition of an ARB to ACE inhibitor

therapy. Greater BP reduction was also noted with this approach. Current evidence supports lowering salt intake to less than 100 mmol (<2.4 g) per day of Na^+ to achieve these clinical end points.

HYPERURICEMIA

CKD patients often develop hyperuricemia and/or gout from their reduced GFR, diuretics, and other abnormalities. An association between hyperuricemia in the setting of CKD and both negative cardiovascular outcomes progression of CKD is noted.[25]

Reduction of symptomatic or asymptomatic hyperuricemia with the use of xanthine oxidase inhibitors, such as allopurinol, may slow loss of kidney function in CKD patients with and without diabetes mellitus. In one study, this effect was independent of other risk markers, for example, albuminuria.[34] Other uric acid-lowering drugs, such as rasburicase and losartan, are associated with improved outcomes in CKD. In an 8-week study comparing rasburicase and placebo, a single 4.5-mg dose of rasburicase significantly lowered serum uric acid levels and improved kidney function. The ARB losartan, by virtue of its ability to increase urinary excretion of uric acid, lowered serum uric acid levels and reduced doubling of serum creatinine or development of ESRD.

OBESITY

Obesity is considered an independent risk factor for CKD. A meta-analysis of weight loss interventions in obese CKD patients showed an association between weight loss and a decrease in both proteinuria and systemic arterial pressure, with no demonstrable decrease in GFR during a mean follow up of 7.4 months. Weight loss interventions were shown to decrease proteinuria and albuminuria by 1.7 g and 14 mg, respectively.[35] These effects were independent of BP reduction.

SMOKING

Tobacco smoking may injure the kidney through various pathways. Hypertension complicates smoking, a well-known factor associated with kidney disease.[25] Smoking also increases SNGFR and may promote progression of kidney disease through hyper-filtration and glomerular capillary hypertension. Finally, smoking raises aldosterone levels. As discussed previously, aldosterone may enhance kidney disease by increasing BP and direct profibrotic effects. In humans, smoking similarly injures the kidney and increases the risk of developing albuminuria in diabetics. Smoking cessation slows progression of kidney disease in patients with diabetic nephropathy and some nondiabetic forms of kidney disease. Given the overall negative health consequences associated with smoking, patients with CKD should be aggressively counselled to quit.

COMPLICATIONS OF CKD

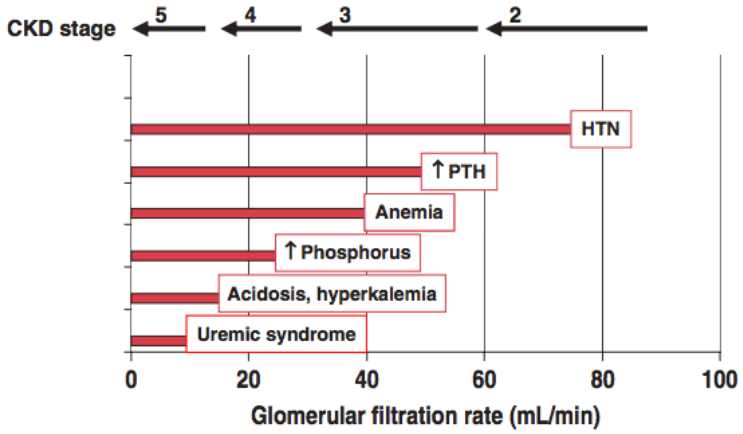


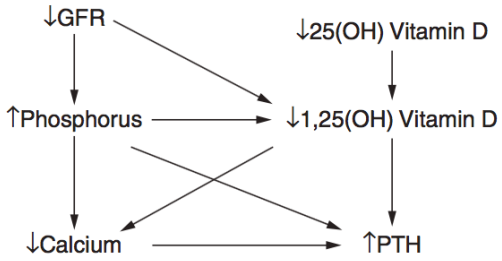
Figure 5 : Complications of CKD by eGFR and Stage of CKD

CARDIOVASCULAR COMPLICATIONS IN CHRONIC KIDNEY DISEASE

Patients with CKD experience greater morbidity and mortality from CVD in comparison to the general population. Roughly 80% of patients with CKD die, primarily of CVD, before reaching the need for dialysis. Of those undergoing dialysis, 45% will die of a cardiovascular cause.[36] The precise biologic mechanisms for this enhanced mortality are unclear but may have to do with the uremic milieu including abnormal phosphorus and calcium homeostasis, increased burden of oxidative stress, increased vascular reactivity, increased left ventricular hypertrophy, and underlying coexistent comorbidities such as hypertension and diabetes mellitus.[37]

DISORDERS OF MINERAL METABOLISM IN CHRONIC KIDNEY DISEASE

The metabolic bone disease of CKD refers to the complex disturbances of calcium and phosphorus metabolism, parathyroid hormone (PTH), active vitamin D, and possibly fibroblast growth factor-23 (FGF-23) homeostasis (see Figure below).



Mineral abnormalities of chronic kidney disease (CKD). Decline in glomerular filtration rate (GFR) and loss of renal mass lead directly to increased serum phosphorus and hypovitaminosis D. Both of these abnormalities result in hypocalcaemia and hyperparathyroidism. Many CKD patients also have nutritional 25(OH) vitamin D deficiency.

A typical pattern seen as early as CKD stage 3 is hyperphosphatemia, hypocalcaemia, and hypovitaminosis D, resulting in secondary hyperparathyroidism.[38] These abnormalities can cause vascular calcification, which may be partly responsible for the accelerated CVD and excess mortality seen in the CKD population. Epidemiologic studies in humans show an association between elevated phosphorus levels and increased risk of cardiovascular mortality in early CKD through ESRD.

HYPERKALEMIA IN CHRONIC KIDNEY DISEASE

Potassium balance generally remains intact in CKD until stages 4–5. However, hyperkalaemia may occur at earlier stages when certain conditions are present, such as type 4 renal tubular acidosis (seen in patients with diabetes mellitus), high potassium diets, or medications that decrease renal potassium secretion (amiloride, triamterene, spironolactone, eplerenone, NSAIDs, ACE inhibitors, ARBs) or block cellular potassium uptake (beta-blockers).[16] Other causes include acidemic states, and any type of cellular destruction causing release of intracellular contents, such as haemolysis and rhabdomyolysis.

ACID–BASE DISORDERS IN CHRONIC KIDNEY DISEASE

Damaged kidneys are unable to excrete the 1 mEq/kg/day of acid generated by metabolism of dietary animal proteins in the typical Western diet. The resultant metabolic acidosis is primarily due to loss of renal mass; distal tubular defects may contribute to or worsen the acidosis.[27] Excess hydrogen ions are buffered by bone; the consequent leaching of calcium and phosphorus from the bone contributes to the metabolic bone disease described above and to growth retardation in children with CKD. Chronic acidosis can also result in muscle protein catabolism, and may accelerate progression of CKD.

NEUROLOGIC COMPLICATIONS IN CKD

Uremic encephalopathy, resulting from the aggregation of uremic toxins, does not occur until GFR falls below 5–10 mL/min/1.73 m^2. Symptoms begin with difficulty in concentrating and can progress to lethargy, confusion, seizure, and coma.[38] Physical findings may include altered mental status, weakness, and asterixis. These findings improve with dialysis.

Other neurologic complications, which can manifest with advanced CKD include peripheral neuropathies (stocking-glove or isolated mononeuropathies), erectile dysfunction, autonomic dysfunction, and restless leg syndrome. These may not improve with dialysis therapy.[27]

ANEMIA OF CHRONIC KIDNEY DISEASE

Anaemia is a common and early complication of CKD. It is characterized by normochromic normocytic RBCs. In 5222 prevalent patients with CKD, mild anaemia, defined as Hb level less than 12 g/dL, was found in 47% of the cohort. The degree of anaemia was most marked in patients with the lowest GFRs. Anaemia however can develop in patients with GFR levels as high as 60 mL/min. Anaemia guidelines for CKD patients recommend anaemia workup and treatment for all Stage 3 or 4 CKD patients. Patients with GFRs less than 60 mL/min/1.73 m^2 and Hb less than 11 g/dL (premenopausal females and pre-pubertal patients) or Hb less than 12 g/dL (adult males and postmenopausal females) should be evaluated. Hb is the recommended parameter for the evaluation and management of anaemia, given the wider variations seen in Hct values and instability of samples.

Anaemia evolves in patients with CKD for a variety of reasons (Table 2). Decreased RBC production, decreased RBC survival, and blood loss all contribute to anaemia. The primary cause of anaemia in patients with CKD is insufficient production of erythropoietin by the diseased kidneys.[39] This is supported by a state of "relative" erythropoietin deficiency in CKD patients, as levels are inappropriately low for the degree of anaemia compared with normal individuals. Finally, an improvement in the RBC count is seen almost uniformly following therapy with exogenous erythropoietin.

Table 3 - Causes of Anemia in Chronic Kidney Disease
Low erythropoietin production
Iron deficiency
Inflammation/infection (cytokines, hepcidin)
Blood loss
Hemoglobinopathies
Severe secondary hyperparathyroidism
Aluminium toxicity
Folate/B 12 deficiency
Shortened red cell survival
Other (hypothyroidism, ACE-inhibitors)

A common secondary cause of anaemia is iron deficiency. Blood loss from phlebotomies associated with laboratory testing, occult gastrointestinal bleeding, decreased iron absorption, dietary restriction, and iron usage by exogenously stimulated erythropoiesis all contribute to the development and maintenance of iron deficiency. In an analysis of data from the NHANES III, 38.3% of 3453 anaemic subjects with GFRs between 20 and 60 mL/min/1.73 m^2 had TSAT (transferrin saturation) values below 20%. Thus, all potential causes of iron deficiency must be fully evaluated in CKD patients. Acute and chronic inflammatory conditions (including infections) are another common cause of anaemia and/ or reduced response to ESA therapy in CKD and ESRD patients (Figure 2). Increased cytokines produced by these conditions reduce ESA response by RBC precursors and also increase production of hepcidin, which sequesters iron in the reticuloendothelial system and induces a functional iron deficiency.[40,41] Other secondary causes of anaemia in CKD include

hypothyroidism, severe hyperparathyroidism, aluminium toxicity, folate and B 12 deficiencies, shortened RBC survival, and haemoglobinopathies.

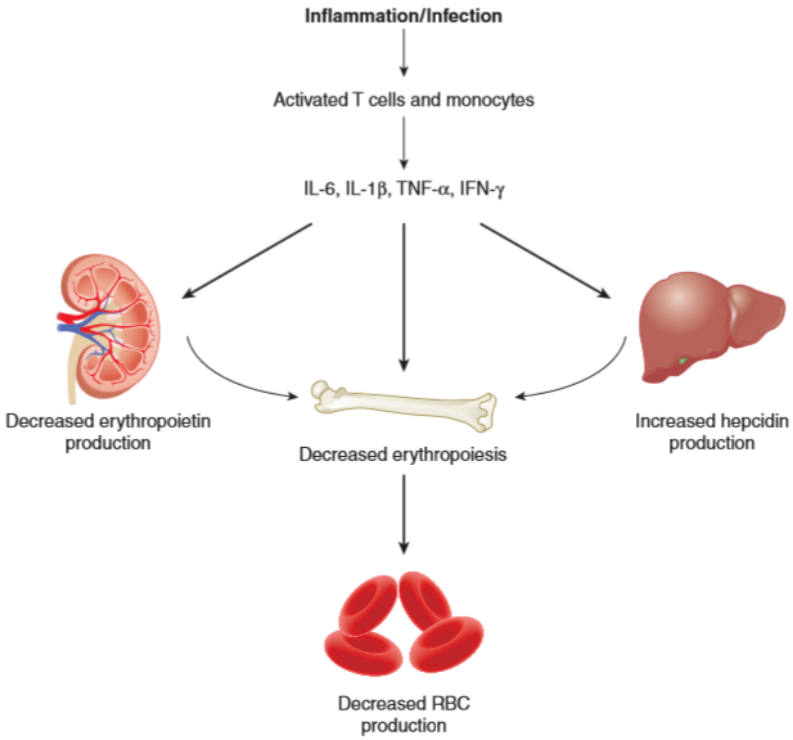


FIGURE - 6 : Effects of inflammation on development of anaemia. Cytokine production stimulated by inflammation/infection decrease RBC production by reducing erythropoietin production, decreasing marrow response to erythropoietin, and increasing hepcidin production, which sequesters iron in the reticuloendothelial system, inducing a "functional" iron deficiency. Abbreviations: IL, interleukin; IFN, interferon; RBC, red blood cell; TNF, tumour necrosis factor. (Courtesy of Mark A. Perazella.)

Evaluation of anaemia in CKD patients should include the following tests:

- Hb and/or Hct
- RBC indices
- Reticulocyte count
- A test for occult blood in stool

- Iron parameters: serum iron, total iron-binding capacity (TIBC), percent transferrin saturation, and serum ferritin.

Diagnosis of iron deficiency is not always straightforward in CKD patients. Functional iron deficiency, which refers to the imbalance between iron needed to support erythropoiesis and the amount released from storage sites, is often present. Serum ferritin values equal to or less than 30 ng/mL indicate severe iron deficiency, and are indicative of absent or low bone marrow iron. Values above 30 ng/mL have to be interpreted with caution because serum ferritin is a known acute phase reactant and can be affected by inflammatory processes.[40] Thus ferritin can be elevated in CKD patients, particularly those on maintenance dialysis, in whom subclinical inflammation is common. TSAT generally reflects the amount of available iron necessary to support erythropoiesis. It is obtained by the formula: (serum iron/TIBC) × 100. Measurement of serum hepcidin levels is not clinically available and levels are not currently superior to standard iron tests.[42] A ferritin concentration below 100 ng/mL is usually diagnostic of iron deficiency; however, the ferritin level may be elevated secondary to chronic inflammation or infection. Thus it is not always a reliable index of iron deficiency in CKD patients. TSAT is considered the best routinely available test of iron deficiency. A TSAT less than 20% usually indicates functional iron deficiency. Other tests, such as the proportion of hypochromic RBCs (>10% with corpuscular Hb <28 g/dL) and reticulocyte Hb content may improve the diagnosis of functional iron deficiency in CKD patients.

EFFECTS OF ANAEMIA IN CHRONIC KIDNEY DISEASE PATIENTS

Anaemia plays a major role in the quality of life in CKD patients and has pronounced effects on patient well-being. It may ultimately determine prognosis both prior to and after starting RRT. For these reasons, it is imperative that anaemia is addressed and judiciously corrected in CKD patients, utilizing an individualized approach and not a fixed Hb target. The relationship between anaemia and morbidity and mortality in dialysis patients is established by observational studies, but correction with ESAs has not improved these outcomes.[43] As previously discussed, observational evidence similarly associates anaemia and CVD in CKD patients. The effect of anaemia on CVD appears to start many years prior to the development of ESRD. However, as in ESRD patients, anaemia correction with ESAs in CKD patients is complicated and a judicious approach must be taken.

ROLE OF ANAEMIA IN CARDIOVASCULAR DISEASE AND MORTALITY

Evidence supports a link between anaemia and CVD. Anaemia is independently associated with the presence of LVH in CKD patients and plays a significant role in its evolution. Evidence in fav or of the connection of anaemia and LVH includes data generated from a cross-sectional study of 175 patients with mean CrCl of 25.5 mL/min. A decline in Hb of 1 g/dL was associated with a 6% independent increased risk for LVH.[43] More severe LVH is seen with lower Hb levels. Anaemia may also increase oxidative stress. Other factors peculiar to CKD such as the uremic milieu, calcification, hypertension, and volume overload contribute to the maladaptive cardiac response to anaemia. Cardiac fibrosis and potentially irreversible LVH may result from these factors. Several observational studies document that

correction of anaemia in ESRD patients reduces left ventricular mass index, improves ejection fraction (EF), and mitigates ischemic changes that develop during stress tests.[44] Similar limited data are available in CKD patients, although small numbers of patients with severe LVH and advanced kidney disease were studied.

OTHER BENFITS OF ANAEMIA CORRECTION

Correction of anaemia in CKD patients includes other benefits such as the following:

1. Improved sense of well-being, quality of life, neurocognitive function, and work capacity (primarily observational studies).

2. Reduced need for packed RBC transfusion.

3. Reduced allo-sensitization pre-transplantation.

4. Reduced hospitalization (observational studies only).

EFFECT OF ANAEMIA CORRECTION ON KIDNEY FUNCTION

Worsening of kidney function with anaemia correction by recombinant human erythropoietin (rHuEpo) was an initial concern based on data from an animal model of kidney disease.[45] Uncontrolled hypertension rather than correction of anaemia was the probable cause of worsening kidney function. Studies in humans uniformly show no effect of

exogenous erythropoietin therapy on renal function in CKD patients. Of interest, a beneficial effect of anaemia correction on renal function was noted in small, uncontrolled studies. Correction of anaemia slowed the progression of CKD and the potential mechanisms for such a desirable benefit was speculated to be a result of correction of anaemia/hypoxia-induced interstitial fibrosis and the anti-apoptotic effect of erythropoietin. Several in vitro studies also supported a kidney protective effect of erythropoietin. However, RCTs do not support a reno-protective effect of ESAs in patients with either CKD or acute kidney injury (AKI). Thus, anaemia correction with these drugs is neither harmful nor beneficial to kidney function in CKD patients.

EFFECT OF ANAEMIA CORRECTION ON BLOOD PRESSURE CONTROL

Anaemia correction with ESAs may increase BP in CKD patients. Concerns for severe hypertensive crisis and seizures were prominent following initial experience with rHuEpo. The increase in BP that develops with ESA is caused by an increase in systemic vascular resistance as well as direct and indirect pressor effects of the drug. These initial concerns, however, were almost entirely alleviated when the rate of Hb correction was slowed to an average of 1g/dL/month. Because hypertension may still develop with slower rates of anaemia correction, BP monitoring should be a standard part of ESA therapy. BP control is easily achieved with adjustments in antihypertensive regimens.

Recombinant human erythropoietin and darbepoetin both successfully correct anaemia in patients with CKD. Optimal target Hb levels are unknown. The Hb targets have changed numerous times as observational data were corrected by the publication of RCTs. Initiation and maintenance dosing of ESA therapy in CKD patients must balance the benefits of improving anaemia-related symptoms and reducing RBC transfusions with the potential harms of stroke and hypertension.[46] Although there is no clear consensus regarding actual target Hb levels in CKD patients (who are not on dialysis), the latest Food and Drug Administration (FDA) guidelines recommend initiation of ESA therapy when Hb is less than 10 g/dL, and decreasing it or interrupting the dosing regimen when it is greater than 10 g/dL. This dose adjustment should take into consideration other factors such as symptoms, comorbid conditions, requirements for blood transfusion, and transplantation status. They also recommend that the Hb target should not exceed 13 g/dL. KDIGO clinical anaemia guidelines are similar to the FDA recommendations. KDIGO guidelines suggest initiating ESA therapy for non-dialysis CKD patients when the Hb is less than 10 g/dL, once all other reversible forms of anaemia have been addressed. The guidelines recommend that ESA therapy not be used to maintain Hb above 11.5 g/dL, although individualization is allowed for those who might benefit from a higher level, but never to exceed 13 g/dL. Adjuvant therapies for anaemia, such as vitamins C, D, and E, folic acid, L-carnitine, and pentoxifylline are not recommended.[47]

The above recommendations were based on several RCTs that collectively demonstrated that full correction of anaemia with an ESA was potentially harmful. One of the

earlier RCTs addressed the issue of full correction versus partial correction of anaemia, in ESRD patients on haemodialysis with underlying symptomatic heart failure or IHD. This study was terminated early because of the concern that correction of Hct to normal levels (~40%) was associated with harm in subjects, although some tried to blame intravenous iron as the cause of the harm.[47] A subsequent study using a target Hb of 13.5 to 14.5 g/dL noted a beneficial effect on left ventricle (LV) volume and LV mass index, but a higher (not significant) stroke incidence in those patients who achieved that Hb level with the use of erythropoietin.

Three landmark studies confirmed that a higher target Hb level in CKD patients offered no benefit and was potentially harmful. In the multicentre, randomized, open-label Cardiovascular Reduction Early Anaemia Treatment Epoetin beta (CREATE)[21] study, the high Hb group (13 to 15 g/dL) gained no clinical outcomes benefit and more of them required dialysis as compared with the low Hb group (10.5 to 11.5 g/dL). The U.S. Correction of Haemoglobin and Outcomes in Renal Insufficiency (US CHOIR)[48] study, which was terminated after only 16 months, also demonstrated that a Hb target of 13.5 g/dL in CKD patients was associated with increased risk of the primary composite end point (death, MI, heart failure hospitalization, and stroke) as compared with the group with a Hb target of 11.3 g/dL. Furthermore, there was no improvement in quality of life. Lastly, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)[49] study, the first randomized, double-blind, placebo-controlled trial designed to evaluate the effect of a Hb level of 13 g/dL on the risk of death, cardiovascular events, and progression to ESRD in type 2 diabetics with Stage 3 or 4 CKD, further argued against higher Hb targets. A significant increase in stroke, particularly in those with prior histories of stroke, and increased venous thromboembolic events were noted in the higher Hb group, despite only achieving 12.5 g/dL. Post-hoc analysis of the TREAT study revealed a significantly higher death rate from cancer in those

who received darbepoetin and had an underlying malignancy at baseline. Thus, full correction of anaemia cannot be recommended given the absence of scientific evidence supporting beneficial effects and the potentially harmful clinical outcomes described in the RCTs.

Subcutaneous injection is the preferred route of ESA administration. Self-administration is simple and well tolerated by most patients. Some patients experience minor pain at the site of injection. rHuEpo is usually given on a weekly or twice-weekly basis. More frequent dosing may be required at initiation, depending on the degree of anaemia. After attaining target Hb, many patients may be subsequently maintained on weekly injections. The recommended starting dose of rHuEpo is 50 to 100 U/kg. Dosing changes for rHuEpo should not be done more frequently than every week, whereas the frequency for darbepoetin should be less. Hb is measured on a weekly basis during the initiation phase of therapy and until the target Hb level is attained. Thereafter, biweekly or monthly determinations are usually sufficient.

Darbepoetin is an erythropoietic agent with a longer serum half-life than rHuEpo. It differs structurally from rHuEpo by virtue of its higher sialic acid-containing carbohydrate content, an important determinant of the half-life of these molecules. It is generally given no more frequently than once a week; bi- or triweekly use may be sufficient to correct anaemia. The starting dose for darbepoetin is 0.45 μg/kg weekly or 0.75 μg/kg every 2 weeks for those on dialysis and 0.45 μg/kg at 4-week intervals. Most patients will require either a dose of 25 or 40 μg. The safety profile of this long-acting erythropoietic agent is similar to that of rHuEpo.

As erythropoiesis is stimulated and the marrow produces RBCs, iron stores are rapidly used. Many patients will require iron supplementation to maintain erythropoietic responsiveness. Oral supplementation can be effective for non-dialysis CKD patients, but intravenous iron preparations may be required. The most commonly utilized intravenous iron preparations to replete iron stores in CKD/ESRD patients are sodium ferric gluconate, iron sucrose, and ferumoxytol. Iron indices such as TSAT and ferritin are followed on a regular basis to guide iron administration. KDIGO[20] guidelines suggest initiating iron therapy when TSAT is less than 30% and ferritin is less than 500 ng/mL. The acceptable range for TSAT is between 30% and 50%, and for ferritin, it is between 500 and 800 ng/mL. Iron therapy is unlikely to provide any further benefit by exceeding the upper limits and risks iron overload and perhaps infectious risk. Suboptimal response to ESA therapy includes inflammatory states, gastrointestinal blood loss, and primary hematologic disorders. These should be fully investigated as clinically indicated. Intravenous iron should not be administered to patient with active systemic infections.

When managing chronic anaemia in CKD patients, KDIGO guidelines note that the benefits of RBC transfusions may sometimes outweigh the risks in patients in whom ESA therapy is ineffective (hemoglobinopathies, bone marrow failure, ESA resistance) and the risks of ESA therapy may outweigh its benefits (previous or current malignancy, previous stroke).

INTRODUCTION ABOUT RED BLOOD CELL DISTRIBUTION WIDTH

Red blood cells (RBC), also conventionally known as erythrocytes, are the most common type of blood cell. The main function of these corpuscular elements in vertebrate organisms is to deliver oxygen through the circulatory system from the lung to the peripheral tissues1. In mammals, erythrocytes lack a nucleus and are typically shaped as biconcave disks, flattened and depressed in the center, with a dumbbell-shaped cross section and a torus-shaped rim on the edge of the disk. Erythrocyte volume varies widely across different vertebrate species. In humans, RBCs have a diameter ranging from 6 to 8mm and a thickness of 2mm. The overall (physiologic) volume of an erythrocyte is hence typically comprised between 80 and 100fL, with an overall surface of 136mm^2 approximately[47].

Under particular circumstances, RBCs may be subjected to remarkable increases or decreases in their typical volume. The intrinsic plasticity of the plasma membrane and the relative modest content of intracellular molecules (principally haemoglobin), allows remarkable contraction and expansion of size and volume. Erythrocytes can thus swell up to a 150fL spherical shape (i.e. macrocytosis), or decrease in size to 60fL or even lower (i.e. microcytosis) without significant loss of membrane continuity and cell injury[47]. The degree of heterogeneity of RBC volume, which is traditionally known as anisocytosis, is conventionally quantified by means of a simple equation, in which the standard deviation (SD) of RBC volumes is divided by the mean corpuscular volume (MCV) of the erythrocytes, and then further multiplied for 100, to express data as a percentage. The result of this equation is finally known as RBC distribution width (RDW; Figure 1)[48]. Since the RDW is

mathematically derived from the MCV, its value may be significantly influenced by the average erythrocyte volume (i.e. the MCV). The observation of a RDW value below the conventional reference range is infrequent and clinically meaningless, whereas an increase of the value over an instrument-specific cut-off mirrors the presence of anisocytosis, which may be attributable to the presence of small and large RBCs, or both.[49]

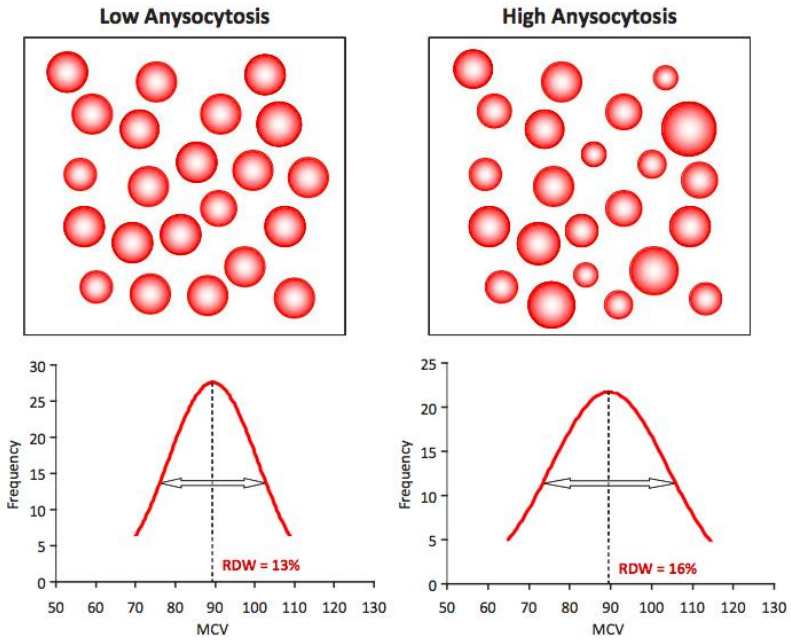


FIGURE - 7 : Relationship between anisocytosis and red blood cell distribution width (RDW)

Physiological determinants of RDW

One of the leading technical issues in routine assessment of RDW is that the reference range is highly analyser-dependent, as will be specifically discussed in this section. As reported by Ricos et al.[50], the within-subject and between subject biologic variations are 3.5 and 5.7%, respectively. Besides pathological causes that may enhance RBC size heterogeneity, which will also be specifically reviewed below, the RDW can vary across a discrete number of physiological conditions (Table 1).

Table 4: PHYSIOLOGICAL DETERMINANTS OF INCREASED RDW
Erythropoietin deficiency and hyporesponsiveness
Ageing
Black ethnicity
Physical exercise
Pregnancy

The hormone erythropoietin, which regulates bone marrow production, maturation and erythrocyte survival[51], is indeed one of the major determinants of RDW. It was in fact proven that both abnormal erythropoietin production and erythropoietin hypo-responsiveness may induce a gradual increase in RDW values.[52,53]

A gradual increase of RDW with ageing has been convincingly reported in the scientific literature. Nearly 10 years ago, Cheng et al. originally described that RDW tended to increase in parallel with age in the very large US National Health and Nutrition Examination Survey III (NHANES III), including approximately 25000 civilian non-institutionalized US citizens, although precise information about this parameter was lacking in the published data[54]. In a further sub-analysis of the NHANES III including 8175 community-dwelling adults aged 45 and older[55], Patel et al. reported that older subjects were more likely to have higher RDW values (highest versus lowest quintile of RDW: 66 versus 58 years). No significant gender differences in RDW values were observed. The positive correlation between age and RDW was confirmed in two subsequent epidemiological investigations. Chen et al. studied 3226 participants aged 35 years and without

cardiovascular disease (CVD) or cancer at baseline[56], and found that subjects in the highest RDW quartile were significantly older than those in the lowest quartile (57 versus 52 years). A marginally but statistically significant increased prevalence of males was also observed when comparing subjects in the highest and lowest quartile of RDW (49% versus 46%). Borne ` et al. measured RDW in 26820 participants in the Malmo ¨ Diet and Cancer study aged 45 years and older (62% females) without history of myocardial injury or stroke[57]. The subjects in the highest RDW quartile were found to be significantly older than those in the lowest (59 versus 57 years). However, no significant sex differences were appreciated across the four quartiles of RDW. More recently, Qiao et al. measured the RDW value in 1259 healthy subjects (584 males and 675 females), and found a consistent trend towards increased values in the elderly[58], with no significant sex differences. In a following investigation in a cohort of 1907 ostensibly healthy blood donors (562 females and 1345 males), Lippi et al. reported that the RDW consistently increased across different age groups, with a median RDW value approximately 11% higher in subjects aged 60 years or older compared to those aged less than 60 years (14.6% versus 13.2%), and nearly 20% higher in the highest age group (490 years; RDW, 15.7%) compared to the lowest age group (541 years; RDW, 13.1%)[59]. Interestingly, the median RDW value was also found to be slightly but significantly higher in the female gender compared to males (13.8% versus 13.3%).

There is only limited information about the potential differences of RDW values among different ethnic cohorts. Saxena and Wong studied 663 whites, 697 blacks, 535 Latin Americans and 247 Asians, and found that RDW values were significantly higher in blacks that in the other ethnical cohorts[60]. Similarly, in the NHANES III study, the prevalence of non-Hispanic blacks was also substantially higher in the highest versus the lowest quintile of RDW values (22% versus 4%), whereas the prevalence of non-Hispanic whites was consequently lower (70% versus 88%)[9]. In a further sub-analysis of the NHANES III study[61], the mean RDW value was found to be significantly higher in Blacks compared to Whites and other ethnicities.

A modest but significant increase in RDW values after physical exercise has been recently reported in three separate investigations, and more specifically after moderate[62], longdistance[63] and exhaustive running[64].

With regard to pregnancy, Shehata et al. longitudinally followed 121 pregnant women from 16 weeks' gestation to 7 days postpartum[65], and reported that the RDW values remained almost unchanged in the period between the 16th and 34th week of gestation, significantly increased between the 34th week of gestation and the onset of labor, but then returned to baseline during the 7 days postpartum. In a separate investigation, Lurie also prospectively followed a group of healthy pregnant women, by assessing RDW between the 12th and the 36th week of gestation and during the latent phase of labor[66]. In contrast with the previous study, a significant increase of RDW could be observed between the 20th and 32nd weeks, whereas the values thereafter declined towards delivery.

Taken together, the available data suggests that erythropoietin stimulation, ageing, black ethnicity, physical exercise and probably pregnancy should be regarded as determinants of increased RDW values, whereas the relationship between anisocytosis and gender appears contradictory across different epidemiological investigations.

Table - 5 : Classification of Anemias according to Values of MCV and RDW.			
RDW VALUE	**Decreased MCV**	**Normal MCV**	**Increased MCV**
Normal	Anaemia of chronic disease	Anaemia of chronic disease	Aplastic anaemia
	Heterozygous thalassemia	Acute blood loss or haemolysis	Chronic liver disease
	Haemoglobin E trait	Anaemia of renal disease	Chemotherapy/antivirals/alcohol
Increased	Iron deficiency	Early Iron deficiency	Immune haemolytic anaemia
	Haemolytic anaemia	Early vitamin B12, folate deficiency	Vitamin B12, folate deficiency
	HbS/Beta Thalassaemia	Transfusions	Hereditary spherocytosis
	Microangiopathic haemolytic anaemia	Chronic hepatobiliary disease	
		Sickle cell anaemia	

RDW IN ERYTHROCYTE DISORDERS

For many years, RDW has been almost exclusively used for the differential diagnosis of anaemias. For practical purposes, the various forms of anaemia are classified according to the MCV value, as microcytic (decreased MCV), normocytic (normal MCV) or macrocytic (increased MCV). The combination of MCV and RDW allows a further sub-classification[67,68], as reported in Table 4. As a general rule, anaemias caused by nutritional deficiencies (such as iron, folate or vitamin B12) tend to be associated with a greater degree of anisocytosis than those caused by genetic defects or primary bone marrow disorders. Although this classification seems helpful to investigate the underlying cause of anaemia, potential overlaps exist among the different conditions, particularly with regard to anaemia of chronic disease.

RDW IN KIDNEY DISEASE

The clinical usefulness of RDW in kidney disease has been investigated in a limited number of studies. Lippi et al.[69]performed a retrospective, cross-sectional study including 8585 adult unselected outpatients, 912 of whom (11%) had impaired renal function as defined by an estimated glomerular filtration rate (EGFR) lower than 60mL/min/1.73m^2.A strong, graded and independent association was found between RDW and EGFR values. In particular the OR for risk of reduced renal function was 1.98 (95% CI: 1.54–2.53) by comparing the lowest versus the highest quartile of RDW, independent of age, gender, MCV and haemoglobin values.

In a following study, Oh et al.[70] performed a retrospective analysis on 470 patients with acute kidney failure who were treated with continuous renal replacement therapy, and reported that RDW was an independent predictor of 28-day all-cause mortality (HR: 1.06; 95% CI: 1.01–1.17) in multivariate Cox proportional hazard analysis after adjustment for age, gender, low mean arterial pressure, haemoglobin, albumin, total cholesterol, CRP and Sequential Organ Failure Assessment (SOFA) score.

Ujszaszi et al.[71] assessed both RDW and EGFR in 723 prevalent kidney transplanted recipients, and found a significant and inverse association between these variables (r¼0.38; p50.001), which remained highly significant after multivariate adjustments for comorbidity, iron deficiency, inflammation and nutritional status. In particular, an increased RDW value (414.0%) was associated with an OR of 1.27 (95% CI: 1.12–1.43) for each 10mL/min decrease in EGFR.

More recently, Solak et al.[72] measured RDW in 367 patients with chronic kidney disease stages from 1 to 5, and reported that RDW values significantly increased from stages 1 to 5, also exhibiting a significant and inverse correlation between EGFR values (r¼0.58; p50.001). Interestingly, RDW was also found to be an independent predictor of endothelial dysfunction assessed with flow-mediated dilatation (beta coefficient, 0.190; p50.001) in stepwise linear regression analysis after adjustment for smoking status, diabetes mellitus, parathyroid hormone, albumin and CRP.

Finally, Mucsi et al.[73] measured RDW in 723 prevalent kidney transplant recipients, who were followed up for 3 years. In a fully adjusted Cox regression analysis, a 1% increase in RDW value was associated with a significantly increased risk of 3-year mortality (HR: 1.60; 95% CI: 1.27–2.02). Accordingly, the inclusion of RDW in all-cause mortality prediction models produced a net reclassification improvement (0.189; p50.001).

RDW AND MORTALITY IN THE GENERAL POPULATION

The very first epidemiological investigation on this topic was published by Perlstein et al.[74]. The study was based on 15852 community-dwelling adults aged 20 years and older enrolled in NHANES III. The primary outcome over a mean of period of 8.7 years of follow up was all-cause mortality, whereas secondary outcomes included death due to CVD, cancer and chronic lower respiratory disease. A 1-SD increment in RDW was associated with 23% increased risk of all-cause mortality, 22% increased risk of cardiovascular mortality, 28% increased risk of cancer mortality and 32% increased risk of chronic lower respiratory disease mortality after multiple adjustment for age, sex, race/ethnicity, physical activity level, achieved education level, smoking status, packyears of smoking, body mass index, systolic blood pressure, hypertension, glycated haemoglobin, diabetes mellitus, hypercholesterolemia, chronic kidney disease and estimated glomerular filtration.

During the same year, a sub-analysis of the NHANES III was also published, including 8175 community-dwelling adults aged 45 and older[55]. The primary outcome over a mean of period of 7.9 years of follow up was all-cause mortality, whereas secondary outcomes included death due to CVD, cancer and chronic lower respiratory disease. After stratification of the study population according to quintiles of RDW, subjects in the highest quintile of RDW had a 2.0-fold higher risk of all-cause mortality, 2.1-fold higher risk of cardiovascular mortality, 1.7-fold higher risk of cancer mortality and 2.0-fold higher risk of mortality for other causes compared to those in the lowest quintile after multiple adjustment for age, sex, ethnicity, education, body mass index, smoking status, cancer, congestive heart

failure, diabetes, heart attack, pulmonary disease, stroke, overnight hospitalization, EGFR, haemoglobin, MCV and CRP.

In another separate publication from the NHANES III study including 15460 subjects aged 20 years and older free of CVD or diabetes[61], the RDW was found to be a significant predictor of mortality (highest versus lowest quartile) in both women (HR for all-cause mortality: 1.22 and 95% CI: 1.14– 1.31; HR for CAD death: 1.17 and 95% CI: 1.07–1.28; HR for cardiovascular death: 1.18; 95% CI: 1.03–1.35) and in men (HR for all-cause mortality: 1.29 and 95% CI: 1.20–1.38; HR for CAD death: 1.25 and 95% CI 1.13–1.39; HR for cardiovascular death: 1.27 and 95% CI: 1.17–1.37).

One year thereafter, Chen et al. measured RDW in 3226 adults aged 35 years and older residing in a suburban township north of Taipei City, Taiwan, who were followed up for a mean period of 15.9 years[56]. The primary outcome was all-cause mortality, whereas secondary outcomes included death due to CVD or to other causes. After stratification of the study population according to quintiles of RDW, subjects in the highest compared to those in the lowest quintile of RDW had a 46% higher risk of all-cause mortality, 45% higher risk of cardiovascular mortality and 46% higher risk of non-cardiovascular mortality after multiple adjustment for age, sex, body mass index, smoking, history of diabetes, hypertension, total cholesterol, triglycerides, albumin, eGFR, RBC count, haemoglobin and MCV. Interestingly, these associations remained significant in both anaemic and non-anaemic individuals.

Lam et al.[75] performed a longitudinal study on 36226 elderly US citizens (65 years and older) observed at an outpatient clinic. The RDW was measured within 3 months of the initial visit and the maximum period of follow up for all-cause mortality was 10 years. Patients with RDW >16.6% had an age, haemoglobin and gender-adjusted 2.3-fold higher risk of all-cause mortality than those with RDW values 16.6%. Interestingly, the risk was found to be higher in non-anaemic than in anaemic subjects (HR: 3.7 versus 1.9).

More recently, Horne et al.[75] investigated the predictive role of RDW for all-cause mortality among 17197 CVD-free subjects enrolled for up to 5 years in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), and who were followed up for a mean period of 1.9 years. In multivariable analysis adjusted for age, sex, low density lipoprotein (LDL)-cholesterol, HDL cholesterol, CRP, family history of CVD, smoking, race, creatinine, glucose and trial drug assignment, the RDW was found to be significantly associated with a 46% higher risk of all-cause mortality, but not of cardiovascular mortality.

RDW AND HUMAN PATHOLOGY: CAUSE OR EFFECT?

Although reliable evidence has been provided about the clinical significance of RDW in health and disease, an open question remains: is anisocytosis a risk factor or a simple epiphenomenon (e.g. a ‘‘marker’’) of an underlying biological or metabolic imbalance? Although a simple and unequivocal answer to this question cannot be given so far, some considerations can be made.

RDW AS A BIOMARKER OF HUMAN DISORDERS

It is rather unquestionable that several biological and metabolic abnormalities associated with human disorders may also exert a considerable influence on erythropoiesis (Table 5). In general, shortening of telomeres (i.e. the DNA-protein structures located at the ends of chromosomes) length is a hallmark of cellular aging and is associated with several age-associated human disorders such as heart disease, diabetes, cancer and infections, along with overall mortality[76]. Kozlitina and Garcia recently assessed the telomere lengths of genomic DNA isolated from circulating white blood cells of 3157 subjects aged 18 years and older participating to the large multi-ethnic Dallas Heart Study[77], and found that shorter telomere lengths were significantly and independently associated with increased RDW values after multiple adjustment for age, gender and ethnicity. Short or critically short telomeres lead to cell senescence of hematopoietic progenitors, especially those of the erythroid lineage, thus leading to increased replicative stress and impaired maturation of the erythroid lineage. It is therefore not unexpected that increased RDW may be significantly associated with ageing as well as with other conditions that are characterized by telomere shortening.

TABLE 6 : Biological and metabolic imbalances contributing to increase anisocytosis	
General	Shortening of telomeres length
	Oxidative stress
	Inflammation
Cardiovascular disease	Dyslipidaemia
	Hypertension
Venous thromboembolism	Poor nutritional status
Cancer	Poor nutritional status
	Erythrocyte fragmentation
Diabetes	Glycosylation of cell surface proteins
	Erythrocyte fragmentation
	Dyslipidaemia
Kidney disease	Decline of erythropoietin synthesis an erythropoietin hypo-responsiveness
	Poor nutritional status
	Erythrocyte fragmentation
Liver disease	Erythropoietin hypo-responsiveness
	Poor nutritional status
	Erythrocyte fragmentation

Oxidative stress is a condition characterized by impairment of balance between oxidants and antioxidant defences, and is associated with enhanced generation of reactive oxygen species and consequent damage to nucleic acids, proteins and lipids. This condition is commonplace in most chronic human disorders, including cancer, diabetes, CVD,

inflammatory disorders, liver failure and chronic kidney disease[54]. Low antioxidant defences are also an independent risk factor for all-cause mortality, as well as non-cardiovascular and cardiovascular death in the general population[55]. Oxidative stress has a profound influence on erythrocyte homeostasis and survival[56]. Accordingly, low serum antioxidant concentrations have been inversely associated with RDW[57]. Therefore, oxidative stress may be another underlying biological mechanism that may lead to increased RDW possibly through increased red cell turnover, thus contributing to the association between anisocytosis and human pathology.

Inflammation is common place in most human disorders and is also the leading mechanism responsible for the presence of anisocytosis in patients with CVD, since several pro-inflammatory cytokines inhibit synthesis or activity of erythropoietin[78]. Atherosclerosis is a multifaceted pathological process that occurs as a result of multiple metabolic derangements, which essentially include dyslipidaemia, inflammation and thrombosis[79]. Since it has been demonstrated that a strong, positive and independent association exists between RDW and conventional inflammatory biomarkers[80], it is plausible that increased anisocytosis may result directly from low-grade inflammation that is commonplace in patients with atherosclerosis[81]. Inflammation might, in fact, promote anisocytosis through impairment of iron metabolism and disruption of response erythropoietin, thus impairing erythrocyte maturation and causing immature erythrocytes to enter the blood flow[82]. Inflammation can also lower erythrocyte survival, thus leading to a more mixed population of RBC volumes in the circulation[83]. It is also noteworthy that RDW was found to be negatively associated with HDL cholesterol, and positively associated with the atherogenic index of plasma, hypertriglyceridemia and the total to HDL cholesterol ratio[84], so that anisocytosis may also be regarded as a marker of dyslipidaemia. Arterial blood pressure is

another potential determinant of RDW value[85,86], and this would also contribute to the link between hypertension, CVD and RDW.

The relationship between RDW and venous thromboembolism is probably multifaceted. It is well established that several nutritional deficiencies occur in patients with chronic immobilization and deterioration of renal function, both of which are characteristic of patients with deep vein thrombosis and/or pulmonary embolism. Hypoxia secondary to obstruction of pulmonary arteries may also cause hyper-activation of both neurohormonal and adrenergic pathways, thus finally triggering the release of pro-inflammatory cytokines[87]. In patients with venous thromboembolism, RDW may hence be elevated as a result of the complex interaction of these underlying conditions.

There are also some plausible explanations that would justify the observation of increased RDW values in cancer patients, and these basically include inflammation and poor nutritional status (e.g. iron, folic acid and vitamin B12 deficiency)[88]. Increased RBC fragmentation is also commonplace in malignancy, especially in patients with metastatic cancer and those undergoing cytotoxic chemotherapy[89]. In cancer patients, therefore, RDW may be regarded as a surrogate biomarker of underlying metabolic abnormalities that are known to predict the clinical outcome.

In regards to diabetes, several structural and functional properties of RBCs are remarkably altered in the presence of hyperglycaemia. These substantially include an increased glycosylation of cell surface proteins, decreased plasma membrane fluidity and

reduced erythrocyte deformability, which would impair the dynamic proprieties of RBCs, complicate their flow through the microcirculation and ultimately increase their vulnerability to injuries[90,91]. Diabetic nephropathy is also associated with erythrocyte fragmentation, which is a well-established cause of anisocytosis[92]. In chronic kidney disease, the gradual decline of erythropoietin synthesis, especially when accompanied by erythropoietin hypo-responsiveness, not only causes a reduced production of RBCs, but is also responsible for the generation of erythrocytes with different sizes, thus ultimately increasing the degree of anisocytosis[52]. Additional factors that would contribute to increase the RDW values in patients with both kidney and liver diseases include increased erythrocyte fragmentation, inflammation, poor nutritional status[93], along with increased oxidative stress.

Several conditions that impair erythrocyte production and survival may be present in patients with liver disease. These basically include down-regulation of erythropoietin receptor expression, nutritional deficiencies (e.g. iron, vitamin B12, folic acid) along with chronic inflammation and increased red cell destruction[115]. Of particular interest is the evidence that the expanded plasma volume associated with portal hypertension in cirrhotic patients may ultimately lead to reduced RBC survival[94], since an enlarged spleen efficiently sequesters and destroys RBC cells.

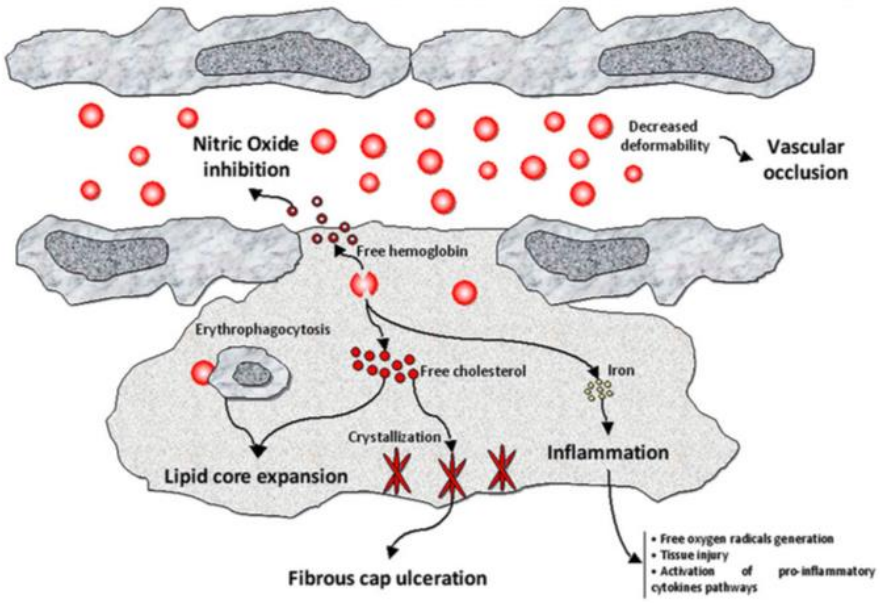


FIGURE – 8 : PATHOPHYSIOLOGY CONTRIBUTING TO ANISOCYTOSIS

RDW AS A CAUSE OF HUMAN DISORDERS

The role of RBC biology in the pathogenesis of some non-hematological disorders has also been recently revaluated, thus opening some intriguing scenarios, where anisocytosis may behave as an active player.

Specifically concerning cardiovascular disorders (Figure 3), Tziakas et al.[95] recently showed that a strong and direct relationship exists between the degree of anisocytosis (i.e. the RDW value) and the cholesterol content of erythrocytes membranes (r¼0.320; p50.001), and that the cholesterol content of erythrocytes membranes is positively and independently associated with clinical instability in patients with cardiovascular disorders[96]. Recent evidence also suggests that the total amount of free cholesterol contained within the necrotic

core of advanced atherosclerotic plaques appears to be much greater than that expected from apoptotic death of inflammatory cells. It is hence conceivable that the free cholesterol in excess within the primary atherosclerotic lesion may originate from other cellular sources, including RBCs[97], and that anisocytosis may directly participate in the pathogenesis of CVD through a variety of mechanisms. The erythrocytes may be entrapped within the atherosclerotic plaque by either injury of the fibrous cap and consequent thrombus formation or due to plaque haemorrhage after injury of intraplaque microvessels. Once entrapped within the atherosclerotic plaque core, RBCs can then contribute to accelerate atherogenesis by a multi-step process. First, the accumulation of free and crystallized cholesterol driving from the erythrocyte membrane, which is reportedly higher in subjects with increased RDW values[95], promotes the expansion of the lipid core (i.e. 50mL of RBC are capable to generate a 0.2-mm3 necrotic core) and the ulceration of the fibrous cap[98]. The iron contained in the haemoglobin molecules released after erythrocyte injury within the atherosclerotic plaque is also effective to trigger a foreign-body reaction, free oxygen radicals generation, tissue injury, and activation of several pro-inflammatory cytokines pathways[99]. Erythrophagocytosis mediated by interaction of RBCs with scavenger receptors on macrophage and other phagocytes may also amplify the formation of foam cells and promote the growth of the atherosclerotic plaque[100]. The neutralization of nitric oxide by cell-free haemoglobin released upon injury of erythrocytes within the necrotic core of the atherosclerotic plaque may also contribute to inhibit endothelium-dependent nitric oxide-mediated vasodilation[101]. Another potential mechanism supporting the pathogenetic role of anisocytosis in CVD is related to the physical properties of RBCs in patients with high degree of anisocytosis. Patel et al.[102] recently showed that an increased RDW is significantly and positively associated with decreased erythrocyte deformability (p¼0.003). It is hence plausible that a greater variation of erythrocyte volumes would increase blood viscosity and

concomitantly impair blood flow through the microcirculation, thus triggering or amplifying the adverse consequences of a pre-existing vascular occlusion in both CVD and venous thrombosis.

The potential causal association of anisocytosis and other non-cardiovascular disorders has been scarcely investigated and seems overall less clear at this point in time. It seems hence reasonable to conclude that increased anisocytosis may be regarded more as a cause rather than an effect in these conditions so far.

After being used for the differential diagnosis of anaemia for decades, the RDW has undergone a notable renaissance in recent years. Increasing and convincing evidence shows that anisocytosis is associated with a variety of human disorders, with their complications and, even more importantly, with overall mortality in the general population (Table 3).

Whether the RDW plays an active role in health and disease or simply behaves as a biomarker, it is increasingly clear that its clinical usefulness should be now broadened beyond its conventional application for troubleshooting anaemia. An increased RDW mirrors a profound deregulation of erythrocyte homeostasis involving both impaired erythropoiesis and abnormal erythrocyte metabolism and survival, which may be caused by a variety of abnormalities, namely, shortening of telomeres length, oxidative stress, inflammation, erythrocyte fragmentation, poor nutritional status, hypertension, dyslipidaemia and abnormality of erythropoietin function. All these conditions are important prognostic factors for severe morbidity and death. It seems hence conceivable that this simple and inexpensive

parameter may provide valuable information about the general health status, the presence of subclinical and clinical diseases, as well as for predicting the prognosis of patients with a variety of frequent acute or chronic conditions. Regardless of the underlying disorder, patients with increased RDW values should hence be more closely and intensively managed to improve their clinical outcomes.

Another important implication that can be inferred from the current scientific literature is that the treatment of anisocytosis itself may be a potential target of future therapies. Despite the lack of interventional studies aimed to investigate the effect of reducing anisocytosis for preventing disease onset and progression, or even for reducing all-cause mortality, it is undeniable that an increased value would still mirror an impairment of one or more important metabolic pathways. Thus, regardless of whether RDW may be regarded as a cause or an effect of human disease, ample interventional studies should be planned to clarify the potential therapeutic implications of lowering RDW in patients with a variety of acute or chronic disorders.

PREPARATION OF THE CHRONIC KIDNEY DISEASE PATIENT FOR RENAL REPLACEMENT THERAPY

When GFR declines to 5–10 mL/min/1.73 m^2 (with or without overt uremic symptoms), renal replacement therapy (haemodialysis, peritoneal dialysis, or kidney transplantation) is required to sustain life.[27] Patient education is important in understanding which mode of therapy is most suitable, as is timely preparation for treatment; therefore,

referral to a nephrologist should take place in late stage 3 CKD, or when the GFR is declining rapidly.[103] Such referral has been shown to improve mortality. Preparation for ESRD treatment requires a team approach with the involvement of dieticians, social workers, primary care clinicians, and nephrologists. For very elderly patients, or those with multiple debilitating or life-limiting comorbidities, dialysis therapy may not meaningfully prolong life, and the option of palliative care should be discussed with the patient and family. Conversely, for patients who are otherwise relatively healthy, evaluation for possible kidney transplantation should be considered prior to initiation of dialysis. [103]

DIALYSIS

Dialysis initiation should be considered when GFR is 10 mL/min/1.73 m^2. Studies suggest that the well-selected patient without overt uremic symptoms may wait to initiate dialysis until GFR is closer to 7 mL/min/1.73 m^2.

Other indications for dialysis, which may occur when GFR is 10–15 mL/min/1.73 m^2 include

(1) uremic symptoms,

(2) fluid overload unresponsive to diuresis, and

(3) refractory hyperkalaemia.

HAEMODIALYSIS (HD)

Vascular access for haemodialysis can be accomplished by an arteriovenous fistula (the preferred method) or prosthetic graft; creation of dialysis access should be considered well before dialysis initiation. An indwelling catheter is used when there is no useable vascular access. Because catheters confer a high risk of blood- stream infection, they should be considered a temporary measure. Native fistulas typically last longer than prosthetic grafts but require a longer time after surgical construction for maturation (6–8 weeks for a fistula versus 2 weeks for a graft). Infection, thrombosis, and aneurysm formation are complications seen more often in grafts than fistulas. *Staphylococcus* species are the most common cause of soft-tissue infections and bacteraemia.

Treatment at a haemodialysis center occurs three times a week. Sessions last 3–5 hours depending on patient size and type of dialysis access. Other haemodialysis schedules can be considered depending on available resources and patient preferences. Home haemodialysis is often performed more frequently (3–6 days per week for shorter sessions) and requires a trained helper. Results of trials comparing quotidian modalities (nocturnal and frequent home haemodialysis) to conventional in-center dialysis have not thus far shown significant mortality differences, but there may be improvements in blood pressure control, mineral metabolism, and quality of life.

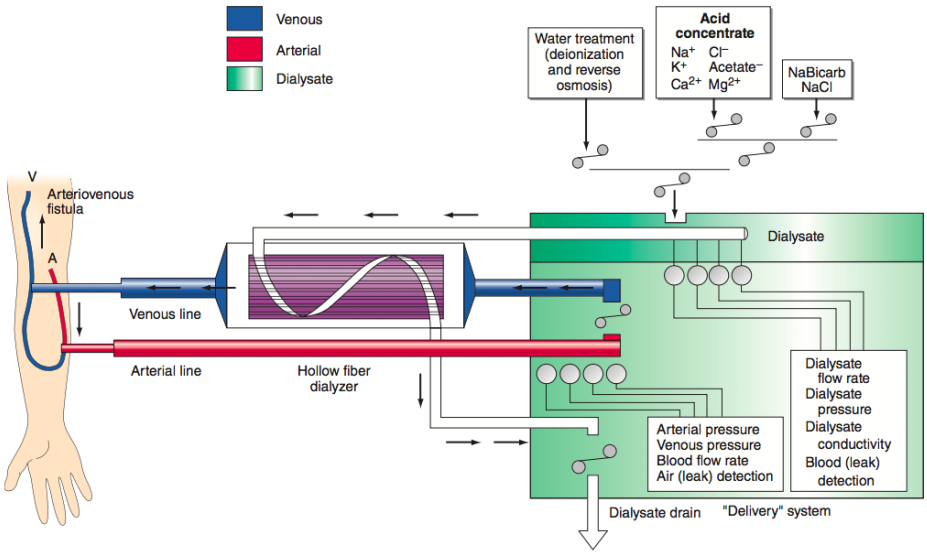


FIGURE – 9 : Schematic Diagram for Haemodialysis **(**A, artery; V, vein)

[Image Courtesy- Harrison's Principles of Internal Medicine 18th edition]

PERITONEAL DIALYSIS (PD)

With peritoneal dialysis, the peritoneal membrane is the "dialyzer." Dialysate is instilled into the peritoneal cavity through an indwelling catheter; water and solutes move across the capillary bed that lies between the visceral and parietal layers of the membrane into the dialysate during a "dwell." After equilibration, the dialysate is drained, and fresh dialysate is instilled—this is an "exchange."

The most common complication of peritoneal dialysis is peritonitis. Peritonitis may present with nausea and vomiting, abdominal pain, diarrhoea or constipation, and fever. The normally clear dialysate becomes cloudy; and a diagnostic peritoneal fluid cell count greater

than 100 white blood cells/mcL with a differential of greater than 50% polymorphonuclear neutrophils. *Staphylococcus aureus* is the most common infecting organism, but streptococci and gram-negative species are also common.

KIDNEY TRANSPLANTATION

Up to 50% of all patients with ESRD are otherwise healthy enough to be suitable for transplantation, although standard criteria for recipient selection are lacking between transplant centers. Older age is becoming less of a barrier, as long as reasonable life expectancy is anticipated. Two-thirds of kidney allografts come from deceased donors, with the remainder from living related or unrelated donors. Over 100,000 patients are on the waiting list for a deceased donor transplant in the United States; the average wait is 2–6 years, depending on geographic location and recipient blood type. The 1- and 5-year kidney graft survival rates are approximately 95% and 80%, respectively, for living donor transplants and 89% and 66%, respectively, for deceased donor transplants.

INITIATION OF RENAL REPLACEMENT THERAPY

Timely initiation of RRT is the final aspect of adequate preparation of the CKD patient. Absolute indications for dialysis include uremic serositis (especially pericarditis), uremic encephalopathy, refractory metabolic acidosis, hyperkalaemia, or uncontrollable volume overload. Initiation of RRT is based on the combination of the presence of signs and symptoms of uraemia, kidney function as assessed by estimated GFR (or CrCl), and patient preference. At the time of initiation of RRT, emotional and physical preparation of patients is key. This approach allows for a smooth transition and more stable entry into ESRD care or pre-emptive transplantation.

Early initiation of RRT for patients with advanced CKD became increasingly accepted as a beneficial approach by the nephrology community based on positive results from observational studies and publication of clinical practice guidelines. Early dialysis was believed to decrease mortality, hospitalizations, and cost of treatment. The Netherlands Cooperative Study on the Adequacy of Dialysis Study Group (NECOSAD) examined 253 patients who started RRT at different GFR levels: timely manner (GFR 7.1 ± 2.4 mL/min/1.73 m ^{2}) and late (GFR 4.9 ± 1.7 mL/min/1.73 m^2). There was a small gain in survival time over 3 years from the time of initiation of RRT in the timely start group (2.5 months), however, there was no significant difference in survival between the 2 groups with long-term follow-up. This and other studies raised questions about the questionable benefit of earlier initiation of RRT.

Subsequently, several observational studies described increased mortality with early start dialysis. As a result of the observational nature of such studies, it was difficult to draw firm conclusions because of problems such as lead-time bias, survivor bias, and inaccuracies of estimating GFR in patients with decreased muscle mass or volume overload. To address the confounding inherent in these studies, a multicentre RCT was conducted among 828 adult patients with progressive CKD. They were randomized to either early (CrCl 10 to 14 mL/min) initiation of RRT or late (CrCl 5 to 7 mL/min) initiation of RRT. No difference in mortality was noted between the early and the late start groups and no difference in the secondary outcomes (cardiovascular events, infectious events and complications of dialysis). The effect of early initiation of RRT on survival was studies in 81,176 relatively healthy ESRD patients. The unadjusted 1-year mortality was 6.8% in those with GFR less than 5 mL/min/1.73 m^2 as compared with 20.1% in those with GFR equal to or greater than 15 mL/min/1.73 m^2, supporting the potential harm associated with early initiation of RRT.

MEDICAL MANAGEMENT OF END STAGE RENAL DISEASE

Some patients are not candidates for transplantation and may not benefit from dialysis. Very elderly persons may die soon after dialysis initiation; those who do not may nonetheless rapidly lose functional status in the first year of treatment.[46] The decision to initiate dialysis in patients with limited life expectancy should be weighed against possible deterioration in quality of life. For patients with ESRD who elect not to undergo dialysis or who withdraw from dialysis, progressive uraemia with gradual suppression of sensorium results in a painless death within days to months. Hyperkalaemia may intervene with a fatal

cardiac dysrhythmia. Diuretics, volume restriction, and opioids, may help decrease the symptoms of volume overload. Involvement of a palliative care team is essential.

PROGNOSIS IN END STAGE RENAL DISEASE

Compared with kidney transplant recipients and age- matched controls, mortality is higher for patients undergoing dialysis. There is likely little difference in survival for well-matched peritoneal versus haemodialysis patients.

Survival rates on dialysis depend on the underlying disease process. Five-year Kaplan-Meier survival rates vary from 37% for patients with diabetes to 54% for patients with glomerulonephritis. Overall 5-year survival is currently estimated at 40%. Patients undergoing dialysis have an average life expectancy of 3–5 years, but survival for as long as 25 years may be achieved depending on comorbidities. The most common cause of death is cardiac disease (more than 50%). Other causes include infection, cerebrovascular disease, and malignancy. Diabetes, advanced age, a low serum albumin, lower socioeconomic status, and inadequate dialysis are all significant predictors of mortality; high fibroblast growth factor (FGF)-23 levels have emerged as a novel marker for mortality in ESRD.

THE FUTURE OF RRT

HD has been called the most successful medical treatment to be introduced during the past century. In contrast to antibiotics, considered by some to be equal to or greater in scope and success, HD always works. It gives indefinite and useful life to anephric persons otherwise facing certain death, usually within a few days. Were it not for the onus of unending dependency on a machine, dialysis therapy would have been considered an unequivocal winner in this best therapy contest. The real and psychologic burden of treatment has been greatly relieved over the past four decades but not eliminated, and in later years, the real burden has actually increased for those seeking the benefits of more frequent treatments. For many of these patients, improvement in health-related quality of life and overall well-being seem to outweigh the increased burden, leading investigators to pursue more objective evidence to sway providers of dialysis therapy. In addition to reducing the burden, the challenges of the future include controlling the accessible risks—including reducing cardiovascular disease, preventing vascular access infections, and managing the legacy of comorbid conditions that affect every patient as he or she initiates long-term dialysis therapy. These conditions differ for each patient, and most require additional and varied treatments that cannot be delivered in the dialysis clinic itself. The physician must partner with multiple specialists, including primary care physicians, who must not be afraid to manage the special needs of dialysis recipients.

One of the challenges is the sheer number of patients in need of kidney replacement.[105] The ever-growing population with CKD in the United States and worldwide

who are likely to require HD in the future presents a challenge to health care providers, who must develop systems to deliver treatments to larger populations in the most cost-effective manner while optimizing treatment outcomes. Achieving the desired improvement in mortality rates would increase the prevalence, thus compounding the problem with numbers of patients despite no change or even a decrease in the incidence of ESRD. These statistical considerations underscore the importance of preventive measures to reduce the prevalence of CKD, thereby allowing limited public resources to better manage patients who need kidney replacement. No one envisioned the massive industry that would spring up from the successes of dialysis therapy and that is sometimes accused of stifling innovation and falling prey to corporate functional fixedness. The challenges to the dialysis industry and provider organizations are to be brave and creative, to ignore the fears of investors and economic advisors, and to put the needs of the patients at the forefront.

The pioneering efforts of Belding Scribner and Willem Kolff were rewarded in 2002 by their joint reception of the Albert Lasker Award for clinical medical research "for the development of renal haemodialysis, which changed kidney failure from a fatal to a treatable disease, prolonging the useful lives of millions of patients." Innovative efforts have also been made in the direction of more compact and more easily managed systems that can be handled by the patient at home. Other workers have sought a much more compact system that can be carried or worn by the patient during dialysis. Advances in sorbent technology, partially from the aerospace industry, have spurred this effort, which could lead to smaller, more compact systems for delivery of both HD and PD.

Successes in the transplantation arena are equally if not more welcome and could change the role of dialysis therapy from that of replacement to that of a bridge to transplantation for many incident recipients. Paired donation and application of extended donor criteria may help extend the availability of transplants to patients previously considered ineligible.

With regard to the measurement and purported adequacy of HD, the Kt/V for urea and its variant measures of small solute clearance remain the most convenient validated measure of the main function of dialysis, which is removal of small solutes. However, dialyzer clearance is not the only determinant of outcome. Multiple factors, including pre-existing cardiovascular disease, diabetic microvascular disease, blood pressure control, severe anaemia, patient compliance, genetic risk factors, and the patient's vascular access, affect survival and health-related quality of life. While we seek to improve dialysis itself, the other modifiable comorbidities must be addressed if outcomes are to improve. Lacking at present is an understanding of how relatively infrequent (thrice-weekly) short applications of artificial clearances compare with continuous native kidney clearances of the same solutes, especially when the solutes are sequestered or protein bound. Likely, the fluctuating and relatively high concentrations of solute and fluid volumes in the patient and the inefficient removal of sequestered or protein-bound solutes contribute to the sluggish immune and inflammatory responses, impaired growth, and susceptibility to malignancies that contribute to morbidity and mortality in today's HD recipients. Sorting out the relative roles of solute toxicity, fluid balance, and unrelated comorbidities remains a major challenge for the next generation.

METHODOLOGY

SOURCE OF DATA:

This study was conducted with 162 Patients diagnosed with CKD in all stages attending the Nephrology unit outpatient section and inpatients of R.L. Jalappa hospital and research centre Tamaka, Kolar.

Inclusion Criteria:

1. Patients aged more than 18 years.
2. Patients diagnosed with Chronic kidney disease.

Exclusion Criteria:

1. Patients with early iron, folate or Vitamin B12 deficiency.
2. Patients with infection, inflammation or chronic immunosuppression
3. Patients with a malignant disease.
4. Patients on cytotoxic chemotherapy
5. Patients who underwent recent surgical procedure.
6. Patients with acute and chronic heart failure, myocardial infarction.
7. Patients with acute pulmonary embolism and peripheral arterial disease.
8. Patients with acute renal failure.

METHOD OF COLLECTION OF DATA

At the time of initial evaluation, the selected patients will undergo a complete clinical history and examination; chest radiograph (postero-anterior or antero-posterior views) at presentation; electrocardiogram; serum electrolyte levels; Urine Analysis, Lipid Profile, complete blood counts, blood urea nitrogen and serum creatinine, serum uric acid Levels, Fasting blood glucose and Ultrasound for Renal echotexture. Informed consent was taken. The estimated glomerular filtration rate was calculated using the abbreviated CKD-EPI formula.

A questionnaire with demographic information, clinical signs and symptoms, laboratory and radiographic findings will be completed for each patient. Patient's daily living abilities were graded according to Eastern Cooperative Oncology Group performance status score (ECOG) ranging from 0-5, with 0 indicating that the patient is fully active and capable for everyday normal activity and 5 indicating that he or she is deceased. ECOG score data collected if combined with RDW has resulted in a reliable prognostic tool.

The baseline demographics and baseline RDW values were collected at the start of dialysis. 2ml venous blood was collected in 2 vacutainers (one with K2 EDTA and other with citrate) .RDW was estimated with an automated haemo-analyser 'Alere h 560'.The reference range for RDW in our laboratory is 11.6–14.9%. The time- averaged RDW values were calculated as the average of the individual RDW values obtained at regular intervals within

the first year of dialysis initiation. The change in RDW was calculated from the regression coefficient between RDW and time, the first year of dialysis initiation. The RDW-slope was defined as the regression coefficient value. The RDW-increased group (Group-A) defined as patients with positive regression coefficient values and RDW-decreased group (Group-B) as those of negative regression coefficient values.

The patient follow-up was performed by means of telephone calls and personal interviews during their visit to our hospital's dialysis unit. The study was approved by the local ethics committee and all patients gave informed consent. The studied end-point was all-cause mortality and correlation with the RDW values. We would like to emphasize that All patients included in the study were treated in accordance with standardized protocols for their disease/condition and that their inclusion in this study had no effect on their treatment, care provided, or the final outcome.

SAMPLING PROCEDURE

A prospective longitudinal study was planned. After obtaining approval from the ethical committee board and taking informed consent, 192 patients aged 18 years or more diagnosed with CKD of various stages were enrolled in the study. Those whose diagnosis changed during the course of treatment or who later fit into the exclusion criteria were excluded.

Figure 10 : Automated Haemo-Analyser 'Alere h 560' with Blood sample Vacutainers

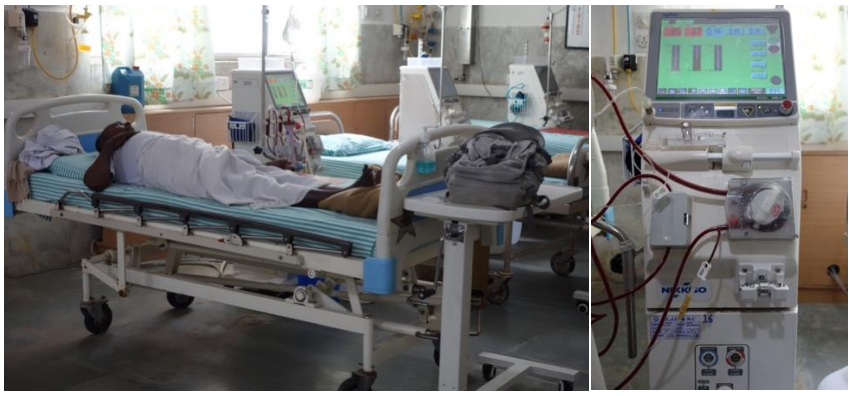


Figure 11 : Patient undergoing Haemodialysis (utilising Nikkiso DBB-27 Dialysis Machine) in the Nephrology unit of RLJH,Kolar.

STATISTICAL ANALYSIS

Sample size is estimated by using the formula[104] :

$n = \frac{2\sigma^2 (Z_{\alpha/2}+Z_{\beta})^2}{(d)^2}$

d: difference in means

Z_{α}:95.1 confidence level : 1.96

Z_{β} : with 80% power : 0.842

Based on a related Indian Study, Sample size of 162 was estimated with each factor and with 80% power and 95% confidence level.

STATISTICAL METHODS:

- Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.[105,106]
- The following assumptions on data is made,

  1.Dependent variables should be normally distributed,

  2.Samples drawn from the population should be random, Cases of the samples should be independent
- Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters.[106]

- Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis.[107]
- The Statistical softwares namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 , Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word 2016 and Excel 2016 have been used to generate graphs, tables etc.

Significant figures

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value:$0.01<P \leq 0.05$)

** Strongly significant (P value : $P \leq 0.01$)

ETHICAL CLEARANCE

Ethical clearance has been obtained from institution ethical committee.

RESULTS

Patients were divided into two groups according to the change in RDW values: an RDW-Increased group A (n = 155) and an RDW-Decreased group (n = 37)

Table 7: Age distribution of patients studied between two groups

Age in years	**Group A** RDW-Increased	**Group B** RDW-Decreased	**Total**
20-30	**2(1.3%)**	**2(5.4%)**	**4(2.1%)**
31-40	**21(13.5%)**	**7(18.9%)**	**28(14.6%)**
41-50	**32(20.6%)**	**10(27%)**	**42(21.9%)**
51-60	**49(31.6%)**	**8(21.6%)**	**57(29.7%)**
61-70	**34(21.9%)**	**7(18.9%)**	**41(21.4%)**
71-80	**15(9.7%)**	**2(5.4%)**	**17(8.9%)**
>80	**2(1.3%)**	**1(2.7%)**	**3(1.6%)**
Total	**155(100%)**	**37(100%)**	**192(100%)**
Mean ± SD	**55.12±12.03**	**51.51±13.82**	**54.42±12.43**

- Majority of subjects in both groups were in the age group of > 51 years. (P=0.114, Not significant)

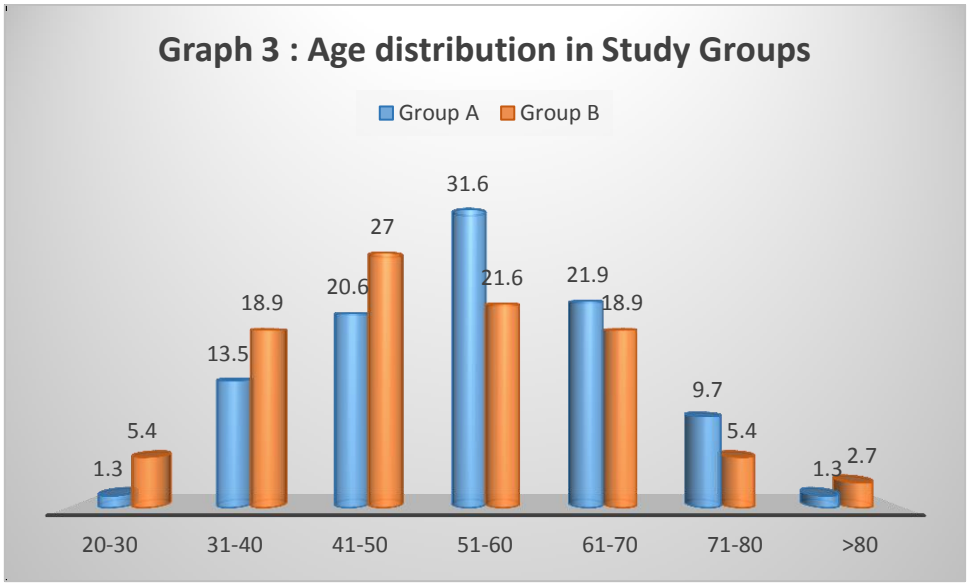


Table 8: Gender distribution of patients between two groups

Gender	Group A RDW-Increased	Group B RDW-Decreased	Total
Female	**40(25.8%)**	**6(16.2%)**	**46(24%)**
Male	**115(74.2%)**	**31(83.8%)**	**146(76%)**
Total	**155(100%)**	**37(100%)**	**192(100%)**

P=0.219, Not significant, Chi-Square test

- In Group-A, females were 25.8% and males being 74%. Group-B contained 16.2% females and 83% males.

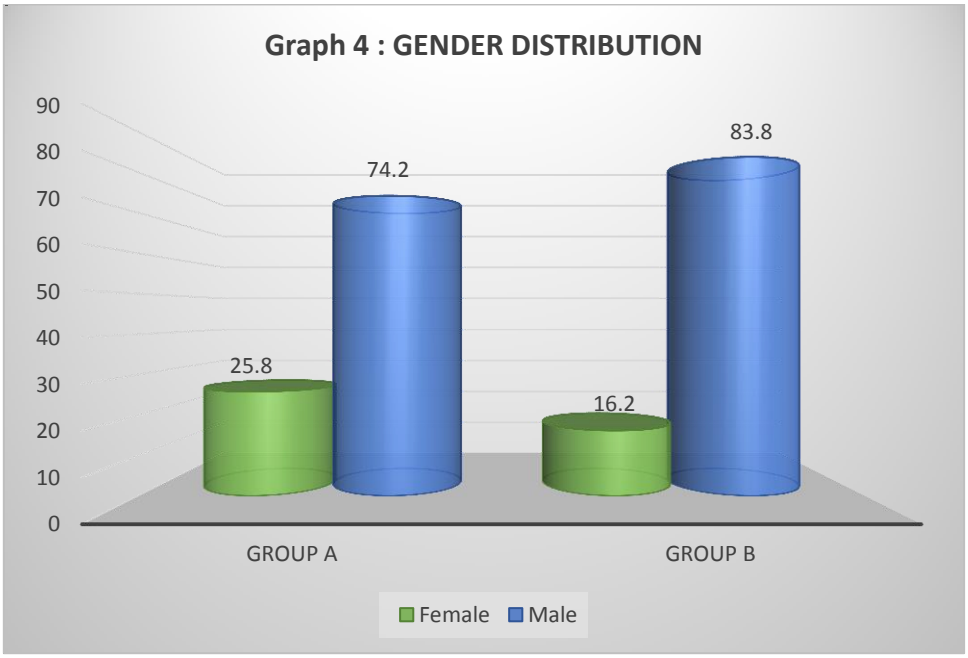


Table 9: Clinical Characteristics of patients Observed in the groups

	Group A RDW-Increased **(n=155)**	**Group B** RDW-Decreased **(n=37)**	**Total (n=192)**	**P value**
Diabetes	**133(85.8%)**	**35(94.6%)**	**168(87.5%)**	**0.177**
Hypertension	**126(81.3%)**	**31(83.8%)**	**157(81.8%)**	**0.724**

Chi-Square test/Fisher Exact test

- In the RDW-Increased group – A patient, 85.8% had Type 2 Diabetes Mellitus and 94.6% in group B. 81.3% of the patients in Group A and 83.8% in group B had Hypertension. There was no significant difference between the two groups.

Table 10: Habits of patients studied

Risk Factors	Group A RDW-Increased (n=155)	Group B RDW-Decreased (n=37)	Total (n=192)	P value
Smoking	**136(87.7%)**	**33(89.2%)**	**169(88%)**	**1.000**
Alcohol	**100(64.5%)**	**28(75.7%)**	**128(66.7%)**	**0.196**

Chi-Square test/Fisher Exact test

- 88%(n=169) of the total number of patients in both groups had smoking habit.
- 66.7%(n=128) of the patients in both groups predominantly of group A (64%) had history of consumption of alcohol.

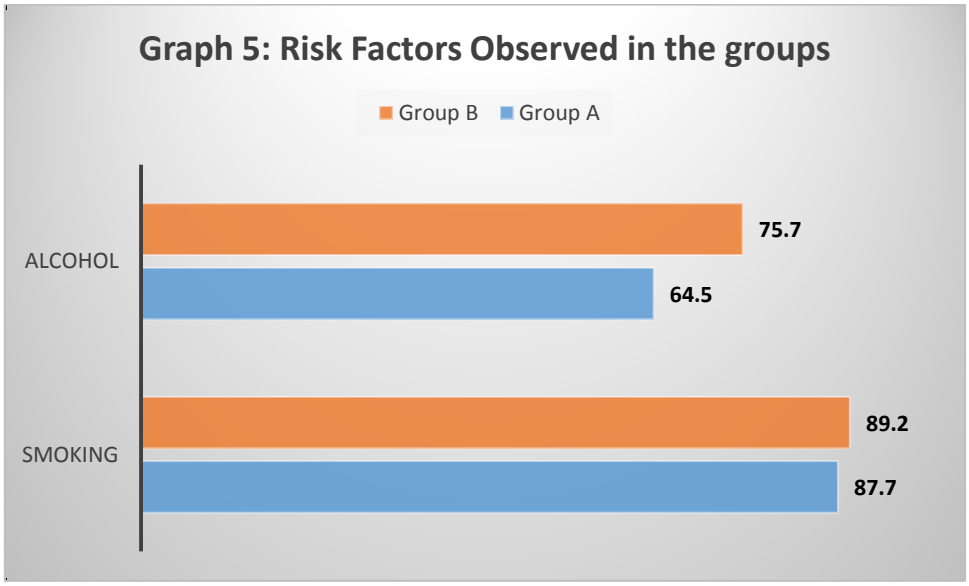


Table 11: Comparison of clinical variables in the groups

	Group A RDW-Increased **(n=155)**	**Group B** RDW-Decreased **(n=37)**	**Total**	**P value**
PR	**81.12±10.62**	**83.30±10.16**	**81.54±10.54**	**0.261**
SBP (mm Hg)	**151.55±18.46**	**156.62±19.46**	**152.53±18.71**	**0.139**
Temp	**98.52±0.31**	**98.51±0.28**	**98.52±0.31**	**0.768**
RR	**25.02±4.17**	**26.08±4.75**	**25.22±4.29**	**0.177**
SpO2 %	**96.10±1.80**	**95.76±1.77**	**96.04±1.79**	**0.292**

Student t test

- There was no significant correlation between the two groups with various clinical parameters such as PR (Pulse Rate), Systolic Blood Pressure (SBP), Temperature (Temp), Respiratory rate (RR) and SpO_2.

Table 12: Correlation between time-averaged Haemoglobin (g/dl) levels compared between the two patient groups

	Group A RDW-Increased **(n=155)**	**Group B** RDW-Decreased **(n=37)**	**Total**	**P value**
First observation	**9.89±1.23**	**9.87±1.19**	**9.89±1.22**	**0.921**
Second observation [after 8th months]	**9.36±1.49**	**9.29±1.41**	**9.35±1.47**	**0.805**
Third observation [after 12 months]	**8.31±2.66**	**9.22±1.95**	**8.48±2.56**	**0.051+**

Student t test

There was no significant correlation between the two study groups in relation to time-averaged haemoglobin levels until the 2nd follow-up which showed positive correlation between the RDW-increased group A (8.31±2.66) and RDW-Decreased group B (9.22±1.95).

Graph 6 : Correlation between time-averaged Haemoglobin (g/dl) levels compared between the two patient groups

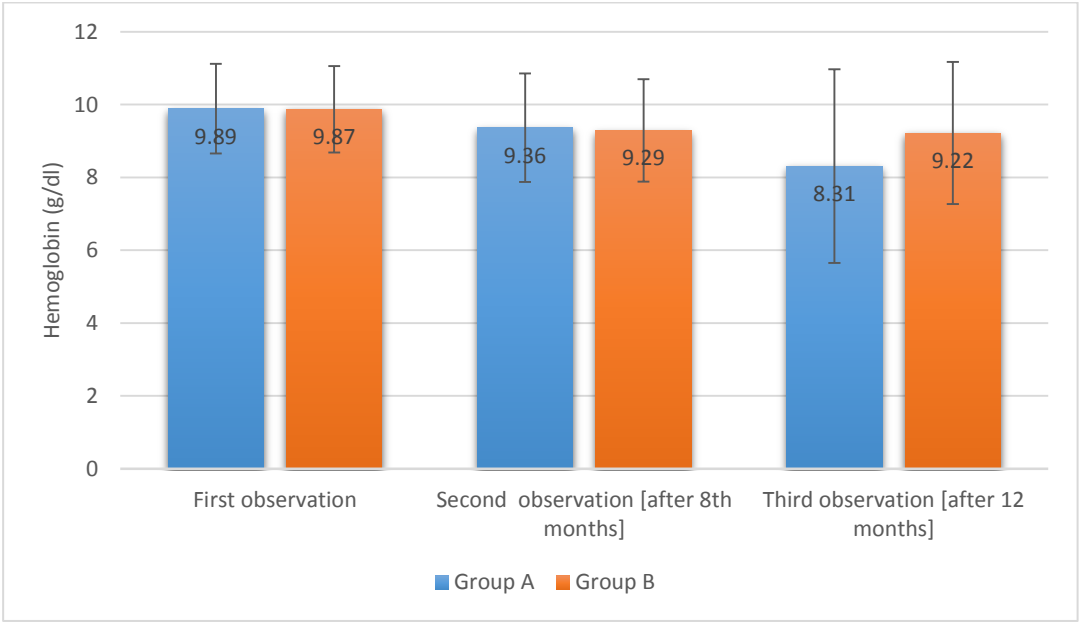


Table 13: Correlation of time-averaged Mean RDW-CV levels in two groups of patients

	Group A RDW-Increased **(n=155)**	**Group B** RDW-Decreased **(n=37)**	**Total**	**P value**
First observation	**13.97±0.61**	**13.86±0.61**	**13.95±0.61**	**0.325**
Second observation [after 8th months]	**14.47±0.85**	**15.00±0.91**	**14.57±0.88**	**0.001****
Third observation [after 12 months]	**15.74±0.76**	**14.26±0.24**	**15.44±0.91**	**<0.001****

Student t test

- There is positive correlation between time-averaged RDW-CV levels in both groups.
- There is progression of raised time-averaged RDW-CV levels observed with each follow-up of the patients.

Graph 7 : Correlation of time-averaged Mean RDW-CV levels in two groups of patients

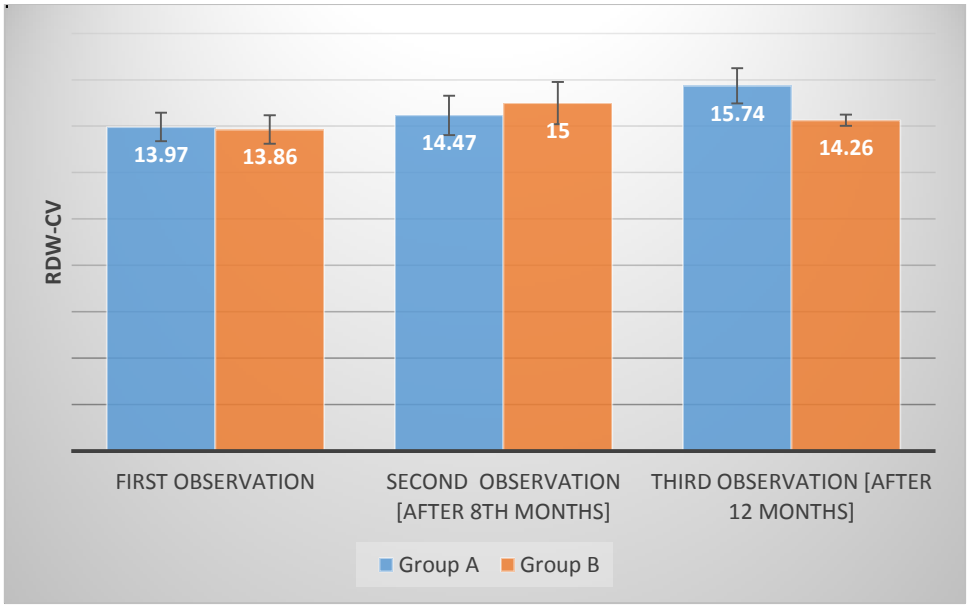


Table 14: time-averaged BUN levels observed in the study groups

BUN	Group A RDW-Increased (n=155)	Group B RDW-Decreased (n=37)	Total	P value
First observation	80.59±10.50	77.73±10.37	80.04±10.51	0.137
Second observation [after 8th months]	82.50±10.27	81.97±10.31	82.40±10.25	0.782
Third observation [after 12 months]	89.16±32.95	97.41±24.38	90.75±31.59	0.154

Student t test

- There was no significant relationship with BUN levels inbetween the two study groups.

Graph 8 : time-averaged BUN levels observed in the study groups

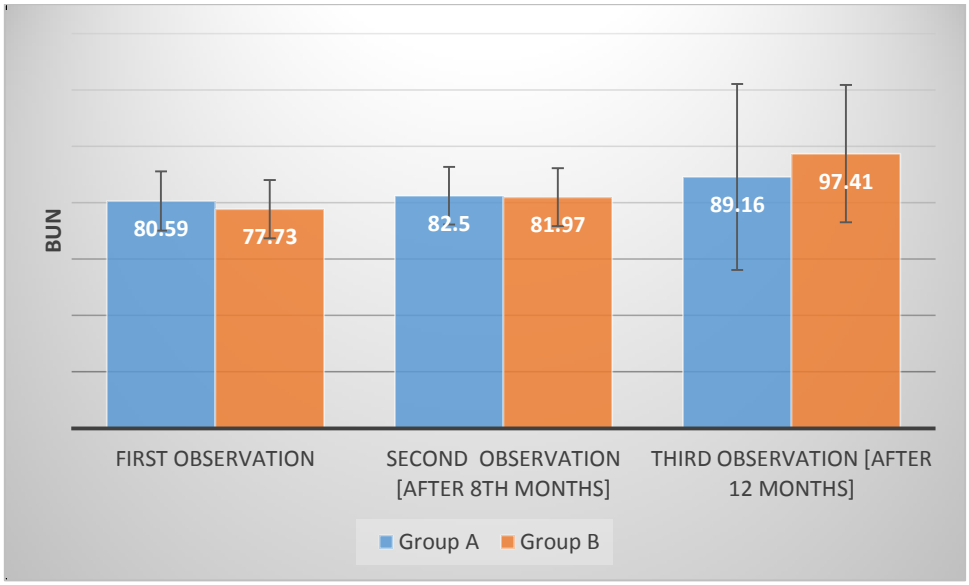


Table 15: time-averaged Serum Creatinine (mg/dl) levels observed in the study groups

Serum Creatinine (mg/dl)	Group A RDW-Increased (n=155)	Group B RDW-Decreased (n=37)	Total	P value
First observation	3.49±1.43	3.42±1.39	3.48±1.42	0.779
Second observation [after 8th months]	3.84±1.76	3.66±1.36	3.81±1.69	0.566
Third observation [after 12 months]	4.69±1.36	5.03±2.12	4.76±1.54	0.238

Student t test

- The time-averaged serum creatinine levels had gradually raised by the 2nd follow-up (4.69±1.36, 5.03±2.12).
- This difference in Serum creatinine levels between the two groups is statically not significant yet correlates with the progression of the disease.

Graph 9 : time-averaged Serum Creatinine (mg/dl) levels observed in the study groups

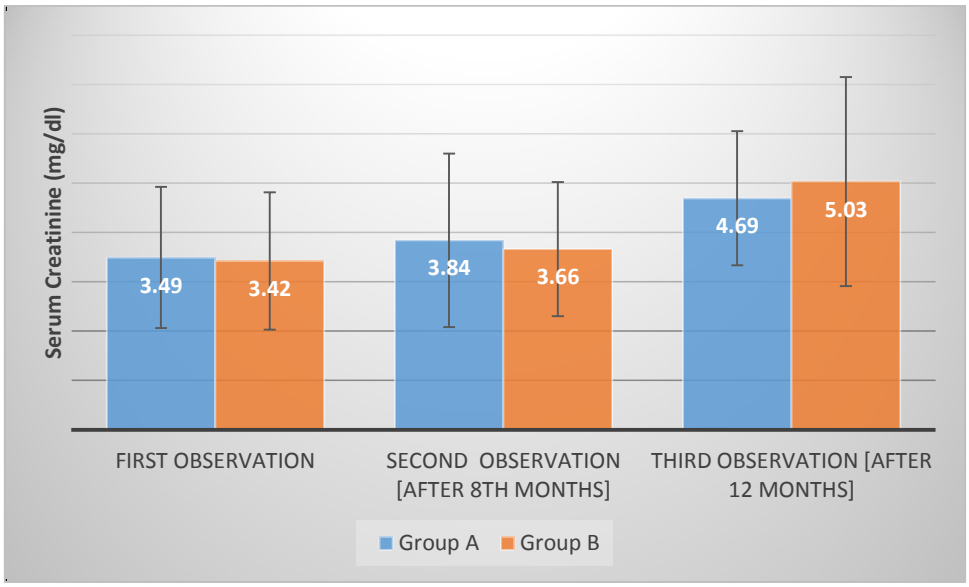


Table 16: Serum Potassium (mEq/l) levels in two groups of patients studied

Serum Potassium (mEq/l)	Group A RDW-Increased (n=155)	Group B RDW-Decreased (n=37)	Total	P value
First observation	5.55±0.29	5.53±0.36	5.54±0.31	0.786
Second observation [after 8th months]	5.51±0.32	5.55±0.26	5.52±0.31	0.450
Third observation [after 12 months]	5.53±0.31	5.40±0.34	5.50±0.32	0.035*

Student t test

In both study groups, there was no significant association with time-averaged serum potassium levels with progression of timeline.

Graph 10: Serum Potassium (mEq/l) levels in two groups of patients studied

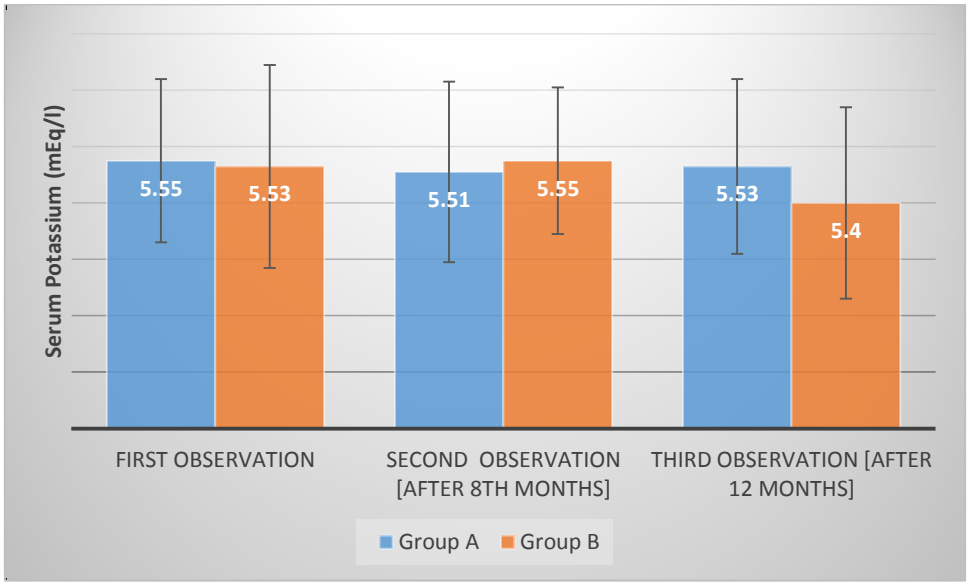


Table 17: Serum Uric Acid levels in two groups of patients

Serum Uric Acid	Group A RDW-Increased (n=155)	Group B RDW-Decreased (n=37)	Total	P value
First observation	5.05±1.18	5.07±1.23	5.06±1.19	0.931
Second observation [after 8th months]	5.26±0.80	5.09±0.58	5.22±0.76	0.247
Third observation [after 12 months]	6.36±0.84	6.62±0.71	6.41±0.82	0.087+

Student t test

- There is significant raise of the time-averaged mean Serum Uric acid levels with progression of time in both study groups predominantly during the 2nd follow-up.(6.36±0.84)
- The Correlation between raised RDW-CV levels and raised uric acid levels with time progression is statistically significant.

Graph 11 : Serum Uric Acid levels in two groups of patients studied

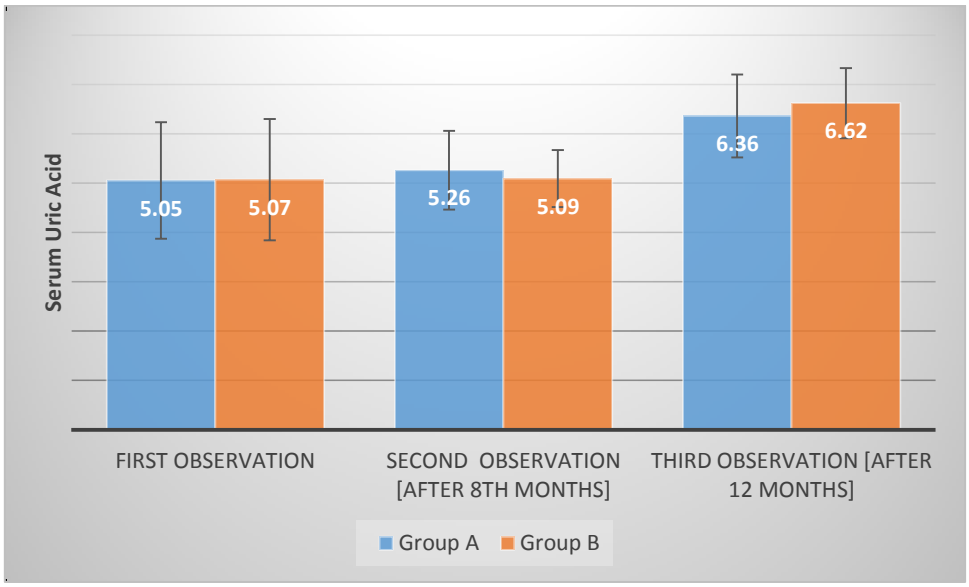


Table 18: mean time-averaged eGFR levels in both study groups

eGFR	Group A RDW-Increased (n=155)	Group B RDW-Decreased (n=37)	Total	P value
First observation	24.21±15.31	24.41±12.80	24.25±14.82	0.943
Second observation [after 8th months]	21.35±12.33	22.31±11.53	21.53±12.16	0.673
Third observation [after 12 months]	14.58±6.47	14.83±6.81	14.63±6.52	0.838

Student t test

- Patients in both study groups had a decline in eGFR during their follow-up of 1 year depicting the progression of CKD.
- There is no significant difference seen in the eGFR values observed during the follow-up period in both study groups.

Graph 12: Mean time-averaged eGFR levels in both study groups

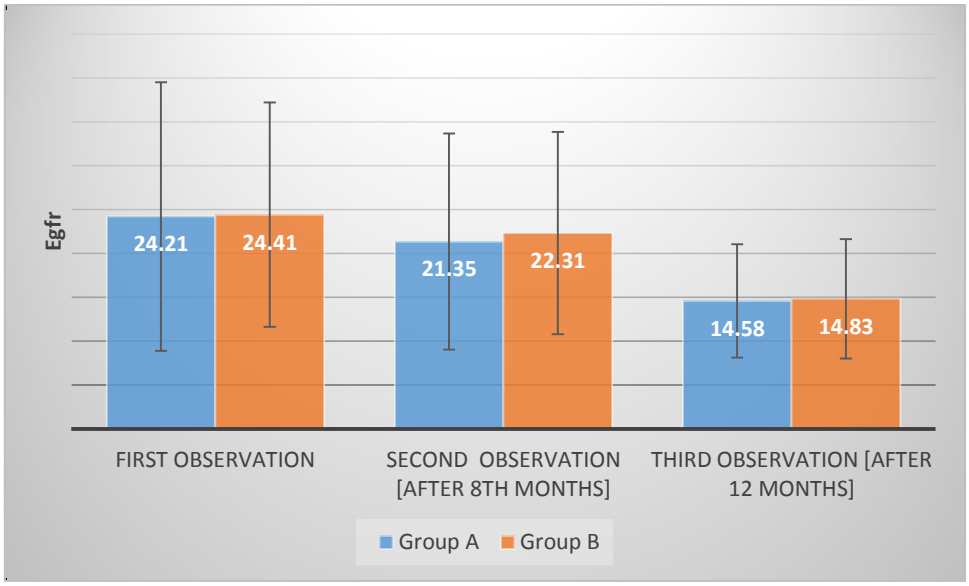


Table 19: CKD Stage distribution in two groups of patients studied

CKD Stage	Group A RDW-Increased (n=155)	Group B RDW-Decreased (n=37)	Total (n=192)	P value
First observation	**155**	**37**	**192**	
• **Stage 1**	**0(0%)**	**0(0%)**	**0(0%)**	
• **Stage 2**	**6(3.9%)**	**0(0%)**	**6(3.1%)**	
• **Stage 3**	**32(20.6%)**	**10(27%)**	**42(21.9%)**	**0.664**
• **Stage 4**	**64(41.3%)**	**16(43.2%)**	**80(41.7%)**	
• **Stage 5**	**53(34.2%)**	**11(29.7%)**	**64(33.3%)**	
Second observation [after 8th months]	**154**	**36**	**190**	
• **Stage 1**	**0(0%)**	**0(0%)**	**0(0%)**	
• **Stage 2**	**0(0%)**	**0(0%)**	**0(0%)**	
• **Stage 3**	**30(19.5%)**	**9(25.0%)**	**39(20.5%)**	**0.700**
• **Stage 4**	**64(41.6%)**	**13(36.1%)**	**77(40.5%)**	
• **Stage 5**	**60(38.9%)**	**14(38.9%)**	**74(38.9%)**	
Third observation [after 12 months]	**141**	**36**	**177**	
• **Stage 1**	**0(0%)**	**0(0%)**	**0(0%)**	
• **Stage 2**	**0(0%)**	**0(0%)**	**0(0%)**	
• **Stage 3**	**6(4.3%)**	**1(2.8%)**	**7(3.9%)**	**1.000**
• **Stage 4**	**41(29.1%)**	**11(30.6%)**	**52(29.4%)**	
• **Stage 5**	**94(66.7%)**	**24(66.7%)**	**118(66.7%)**	

Chi-Square test/Fisher Exact test

- Though statistically not significant, both study groups had showed positive correlation with progression of CKD in relation to declining trend of eGFR values and declining performance status of the patients during the follow-up timeline.
- Patients in the RDW-Increased group A showed significant progression of CKD to ESRD in comparison to RDW-Decreased Group B.

Table 20: ECOG Scores observed in two study groups.

ECOG	**Group A** RDW-Increased **(n=155)**	**Group B** RDW-Decreased **(n=37)**	Total (n=192)	P value
First observation	155	37	192	
0-Asymptomatic	0(0%)	0(0%)	0(0%)	0.406
1-Symptomatic but completely ambulatory	24(15.5%)	6(16.2%)	30(15.6%)	
2-Symptomatic, <50% in bed during the day	69(44.5%)	12(32.4%)	81(42.2%)	
3-Symptomatic, >50% in bed, but not bedbound	47(30.3%)	15(40.5%)	62(32.3%)	
4-Bedbound	14(9%)	3(8.1%)	17(8.9%)	
5-Death	1(0.6%)	1(2.7%)	2(1%)	
Second observation [after 8th months]	154	36	190	
0-Asymptomatic	0(0%)	0(0%)	0(0%)	0.078+
1-Symptomatic but completely ambulatory	6(3.9%)	1(2.8%)	7(3.7%)	
2-Symptomatic, <50% in bed during the day	47(30.5%)	6(16.7%)	53(27.9%)	
3-Symptomatic, >50% in bed, but not bedbound	72(46.8%)	23(63.9%)	95(50%)	
4-Bedbound	16(10.4%)	6(16.7%)	22(11.6%)	
5-Death	13(8.4%)	0(0%)	13(6.8%)	
Third observation [after 12 months]	141	36	177	
0-Asymptomatic	0(0%)	0(0%)	0(0%)	0.040*
1-Symptomatic but completely ambulatory	0(0%)	0(0%)	0(0%)	
2-Symptomatic, <50% in bed during the day	2(1.4%)	2(5.6%)	4(2.3%)	
3-Symptomatic, >50% in bed, but not bedbound	71(50.4%)	10(27.8%)	81(45.8%)	
4-Bedbound	53(37.6%)	18(50%)	71(40.1%)	
5-Death	15(10.6%)	6(16.7%)	21(11.9%)	

Chi-Square test/Fisher Exact test

- With time progression during the follow up period, there is significant decline of the patients performance status (increased ECOG Scores).
- The Patients Performance status decline (gradual increase of ECOG score in time) were significantly correlating with the progressive decline in eGFR and increased RDW-CV values.

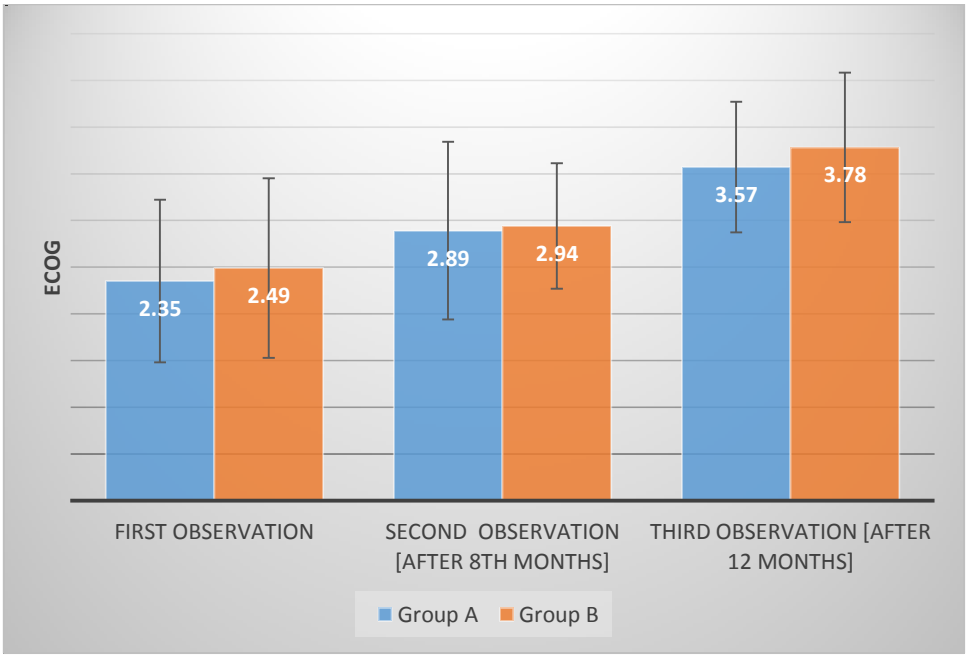
Table 21: Time-Averaged ECOG Scores in two study groups

ECOG	RDW		Total	P value
	Group A	Group B		
First observation	2.35±0.87	2.49±0.96	2.38±0.89	0.397
Second observation [after 8th months]	2.89±0.95	2.94±0.67	2.90±0.90	0.743
Third observation [after 12 months]	3.57±0.70	3.78±0.80	3.62±0.72	0.132

Student t test

- There is progression of ECOG performance status scores of patients in both study groups during the 1 year follow-up period. Out of 192 patients observed in the study, there were 29 deaths.(ECOG score of 5)
- All patients who had died during the study had significantly higher RDW-CV values (n=24) and were in raising trend during their follow-up.

Graph 13: Time-Averaged ECOG Scores in two study groups



DISCUSSION

Patients were divided into two groups according to the change in RDW values: an RDW-decreased group (n = 155) and an RDW-increased group (n = 37).

RDW-increased group had a lower baseline RDW value (13.97±0.61) and higher follow-up RDW value (15.74±0.76) at 1 year than did the RDW-decreased group. Fewer patients in the RDW-increased group had a baseline RDW >14.9% compared with the RDW-decreased group (P < 0.001). However, the time-averaged RDW values did not differ between the two groups. The RDW-increased group had higher levels of BUN, Creatinine and uric acid levels than the RDW-decreased group. Patients in the RDW-Increased group had Higher ECOG scores with follow-up in 1 year compared to the RDW-decreased group.

Patients in both study groups had a decline in eGFR during their follow-up of 1 year depicting the progression of CKD. Predominantly in the RDW-Increased Group A (n=155) the initial time-averaged eGFR was noted as 24.21±15.31 mL/min/1.73 m^2 and the follow-up after 1 year showed significant decline to 14.58±6.47 mL/min/1.73 m^2 respectively. There is no significant difference seen in the eGFR values observed during the follow-up period in both study groups.

During the follow-up, 29 deaths (11.6%) have occurred. The RDW-increased group showed significantly lower event-free survival rates for all-cause death than did the RDW-decreased group (P = 0.001). The event-free survival rates did not differ between patients with a baseline RDW 14.9% and RDW increase and those with a baseline RDW >14.9% and RDW decrease (P <0.001).

ECOG score has been commonly used for years in patients with malignancy, but it can be applied for accurate assessment of daily living abilities in every patient.[110] When we added graded RDW score to ECOG score, we significantly improved prognostic performance of the RDW alone model. Combining a simple clinical assessment tool, such as ECOG score, with RDW resulted in a very reliable prognostic tool, which can be applicable among patients in chronic dialysis in everyday clinical practice. There is progression of ECOG performance status scores[graph-13] of patients in both study groups during the 1 year follow-up period. Out of 192 patients observed, all 29 patients who had died during the study had significantly higher RDW-CV values[table-20] and were in raising trend during their follow-up.(p= 0.040+). These results are in line with those of Hunziker et al,[108] who have proven that adding RDW to SAPS prognostic tool significantly improves prognostic reliability of SAPS score in identifying critically ill patients.

There are several reports in the literature described RDW changes in patients with impaired renal functions. Docci et al.[109] described RDW changes in chronic kidney disease patients for the first time in a preliminary study. In their study, RDW has been found to be increased in chronic HD patients compared to healthy subjects. Data in the literature have suggested the association between RDW and renal functions subsequently.[69] Lippi et al.[79] showed negative and gradual relation between RDW and renal functions in their study group of congestive heart failure patients. They concluded that decreased GFR predicted elevated RDW independent of age, gender, MCV, and haemoglobin. Our results indicating increased RDW associated with progressive decreased renal function in overall study population were correlating with the results of previous studies. [70]

Little is known about the mechanism by which elevated values of RDW are associated with increased mortality. Usually, RDW is elevated when there is increased red cell destruction, or what is more common, ineffective and increased red cell production, which are both prevalent in patients on dialysis. RDW may represent malnutrition, suppression of bone marrow production, or chronic inflammation.[81,82] Although the mainstay of atherosclerosis pathogenesis and progression is chronic inflammation, it is highly unlikely that the relation of RDW to mortality risk is based only on the premise of chronic inflammation.[83]

Association of RDW with all-cause mortality indicates that not only deaths from cardiovascular diseases, but cancer and other causes are all connected to RDW, which is also supported by findings of a meta-analysis on older populations.[71,72]

This study has several limitations. Regardless of the prospective longitudinal design of the study, one year is a rather short follow-up and we would suggest a larger, multicenter study with longer follow-up to make definitive conclusions and evaluate our findings. Despite these limitations, a major strength of this study lies in its prospective design with good follow-up and low drop-out. What is more important, this study is based on real-life "every day dialysis patient" sample.

CONCLUSION

In conclusion, this study demonstrated that RDW is related to progression of CKD and could be an additive predictor for all-cause mortality in patients on chronic dialysis. Available literature data does not provide clear explanations for such a finding, but nevertheless RDW combined with sound clinical judgment, ie, ECOG score improves identification of patients with an increased risk compared to RDW model alone. Since RDW is a simple, inexpensive, and widely available test, the data may have significant clinical implications for assessing prognosis and choice of treatment in patients with CKD. The prognostic strength of a rising RDW may be greater than other expensive and clinically inaccessible markers markers which is another limitation to our study due to unaffordability and inaccessibility to our patients. However, prospective, multicenter studies are needed to observe possible other pathophysiological mechanisms of RDW elevation in ESRD patients.

SUMMARY

This is a prospective longitudinal study conducted in R. L. Jalappa hospital and research centre Tamaka, Kolar. After obtaining approval from the ethical committee board and taking informed consent, 192 patients aged 18 years or more diagnosed with CKD of various stages were enrolled in the study. Those whose diagnosis changed during the course of treatment or who later fit into the exclusion criteria were excluded.

Patients were divided into two groups according to the change in RDW values: an RDW-Increased group A (n = 155) and an RDW-Decreased group (n = 37). RDW-increased group had a lower baseline RDW value (13.97±0.61) and higher follow-up RDW value (15.74±0.76) at 1 year than did the RDW-decreased group. Fewer patients in the RDW-increased group had a baseline RDW >14.9% compared with the RDW-decreased group ($P < 0.001$). However, the time-averaged RDW values did not differ between the two groups. The RDW-increased group had higher levels of BUN, Creatinine and uric acid levels than the RDW-decreased group.

Patients in the RDW-Increased group had Higher ECOG scores with follow-up in 1 year compared to the RDW-decreased group. There is progression of ECOG performance status scores[graph-13] of patients in both study groups during the 1 year follow-up period. Out of 192 patients observed, all 29 patients who had died during the study had significantly higher RDW-CV values[table-20] and were in raising trend during their follow-up (p= 0.040+).

Patients in both study groups had a decline in eGFR during their follow-up of 1 year depicting the progression of CKD. Predominantly in the RDW-Increased Group A (n=155) the initial time-averaged eGFR was noted as 24.21±15.31 mL/min/1.73 m^2 and the follow-up after 1 year showed significant decline to 14.58±6.47 mL/min/1.73 m^2 respectively. There is no significant difference seen in the eGFR values observed during the follow-up period in both study groups.

In conclusion, this study demonstrated that RDW is related to progression of CKD and could be an additive predictor for all-cause mortality in patients on chronic dialysis. Available literature data does not provide clear explanations for such a finding, but nevertheless RDW combined with sound clinical judgment, ie, ECOG score improves identification of patients with an increased risk compared to RDW model alone. Since RDW is a simple, inexpensive, and widely available test, the data may have significant clinical implications for assessing prognosis and choice of treatment in patients with CKD. The prognostic strength of a rising RDW may be greater than other expensive and clinically inaccessible markers which is another limitation to our study due to unaffordability and inaccessibility to our patients. However, prospective, multicenter studies are needed to observe possible other pathophysiological mechanisms of RDW elevation in ESRD patients.

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ANNEXURE - 1

INFORMED CONSENT FORM

Prognostic Value of Red Blood Cell Distribution Width for Patients with Chronic Kidney Disease

Chronic Kidney Disease (CKD) has high incidence in India. It is hoped that the knowledge of relevant prognostic factors might be useful for early identification of patients at high risk requiring intensive care treatment. If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. We will collect the treatment and relevant details from your hospital record. This information collected will be used for only dissertation and publication. The institutional ethical committee has reviewed this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

I understand that I remain free to withdraw from the study at any time and this will not change my future care. I have read or have been read to me and understood the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study. I have had the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction. I,the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for dissertation and publication only.

Subject name & Address: SIGNATURE /THUMB IMPRESSION

(Parents / Guardians name)

DATE:

Name and signature of the Medical Professional receiving consent :

ANNEXURE - 2

PROFORMA

1) **OP/IP No:**
2) **DATE:**
3) **NAME:**
4) **AGE:**
5) **MARITAL STATUS & OCCUPATION:**
6) **ADDRESS:**
7) **CHIEF COMPLAINTS:**

8) **PAST HISTORY:**

9) **FAMILY HISTORY:**

10) **PERSONAL HISTORY:** Smoking/Alcohol/Tobacco/other_____

11) **GENERAL PHYSICAL EXAMINATION:** (AT ADMISSION)

Date						
Pulse Rate						
Blood Pressure:						
Respiratory Rate:						
Temperature:						
Physical Signs (mark observed)	Pallor ☐	Icterus ☐	Cyanosis ☐	Clubbing ☐	Lymphadenopathy ☐	Edema ☐
Jugulular Venous Pressure						

12) **SYSTEMIC EXAMINATION:**

Cardiovascular system:

Respiratory system:

Abdomen:

Nervous system:

13) DIAGNOSIS:

14) Duration of Hospital Stay:

15) INVESTIGATIONS:

Haemogram	HB (g/dl)				
	RDW-SD(fL)				
	WBC				
RFT	B.Urea (mg/dl)				
	Sr.Creatinine (mg/dl)				
Lipid Profile	Cholesterol (mg/dl)				
	Triglycerides (mg/dl)				
	HDL cholesterol (mg/dl)				
Sr.Electrolytes	Sodium (mEq/l)				
	Potassium (mEq/l)				
Ultrasonogram					
EKG					
eGFR (CKD-EPI) ml/min per 1.73m^2					

16) **ECOG Score:**

Date			
ECOG Score			

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Deceased.

17) **Follow up Notes:**

KEY TO MASTER CHART
M - Male Sex
F - Female Sex
s. K – Serum Potassium
s.CREAT - Serum Creatinine
BUN – Blood Urea Nitrogen
SBP – Systolic Blood Pressure
PR – Pulse Rate
TEMP – Axillary Temperature
RR – Resting Respiratory Rate
1 – Presence of the variable
0 – Absence of the variable
Glycated Hb - Glycated Haemoglobin
HB - Haemoglobin
RDW -CV : Red Cell Distribution Width Coeffieient Variation
S. Uric Acid - Serum uric acid
eGFR - estimated glomerular filtration rate

ECOG - Eastern Cooperative Oncology Group Score
0 – Asymptomatic 1 – Symptomatic but completely ambulatory 2 – Symptomatic, <50% in bed during the day 3 – Symptomatic, >50% in bed, but not bedbound 4 – Bedbound 5 – Death
(1) - First observation
(2) - second observation [after 8th months]
(3) - Third observation [after 12 months

CKD Stage	**eGFR level (mL/min/1.73 m^2)**
Stage 1 CKD	≥ 90
Stage 2 CKD	60 – 89
Stage 3 CKD	30 – 59
Stage 4 CKD	15 – 29
Stage 5 CKD	< 15

INTRODUCTION

OBJECTIVES

REVIEW OF LITERATURE

MATERIALS & METHODOLOGY

RESULTS

DISCUSSION

CONCLUSION

SUMMARY

BIBLIOGRAPHY

ANNEXURE