Chronic Kidney Disease Update

Waqar H. Kazmi and Khurram Danial

Karachi Medical & Dental College, Abbasi Shaheed Hospital, Karachi
Pakistan

1. Introduction

Chronic kidney disease (CKD) is a worldwide public health issue. In the United States there is a rising incidence and prevalence of kidney failure with poor outcomes and high cost. Most chronic nephropathies are characterized by a progressive course that leads, at a variable rate, to loss of kidney function and the need for renal replacement therapy. The progression of CKD typically moves through phases from initial diminution of renal reserve to mild, moderate and severe reductions in glomerular filtration rate (GFR), to end-stage renal disease (ESRD). There is growing evidence that some of the adverse outcomes of CKD can be prevented or delayed by preventive measures, early detection and treatment.

2. Definitions and classification

The definition and classification of CKD may help identify affected patients, possibly resulting in the early institution of effective therapy. To achieve this goal, guidelines were proposed from the National Kidney Foundation of the United States through its Kidney Disease Outcomes Quality Initiative (K/DOQI) program (National kidney Foundation [NKF], 2002). These guidelines have been reviewed and accepted internationally (Levey et al., 2005; Uhlig et al., 2005; Levin et al., 2008).

The K/DOQI working group defined CKD in adults as:

- Evidence of structural or functional kidney abnormalities (abnormal urinalysis, imaging studies, or histology) that persist for at least three months, with or without a decreased GFR. The most common manifestation of kidney damage is persistent albuminuria, including microalbuminuria.

  OR

- Decreased GFR (as defined by a GFR of less than 60 ml/min per 1.73 m^2), with or without evidence of kidney damage.

Based upon these definitions, the following is the recommended classification of CKD by stage and the estimated prevalence within the United States of each stage, as determined by a National Health and Nutrition Examination Survey (NHANES) performed in 1999 to 2004 (KDOQI, 2002; Coresh et al., 2003; Levey et al., 2003; Coresh et al., 2005; MMWR, 2007; Coresh et al, 2007).

- Stage 1 disease is defined by a normal GFR (greater than 90 ml/min per 1.73 m^2) and persistent albuminuria (1.8 percent of the total United States population)
- Stage 2 disease is a GFR between 60 to 89 ml/min per 1.73 m^2 and persistent albuminuria (3.2 percent)

- Stage 3 disease is a GFR between 30 and 59 ml/min per 1.73 m² (7.7 percent)
- Stage 4 disease is a GFR between 15 and 29 ml/min per 1.73 m² (0.21 percent)
- Stage 5 disease is a GFR of less than 15 ml/min per 1.73 m² or ESRD (2.4 percent for stages.)

2.1 Estimation of glomerular filtration rate (GFR)

Patients with kidney disease may have a variety of different clinical presentations. Some have symptoms that are directly referable to the kidney (gross hematuria,or flank pain), or to extrarenal symptoms (edema, hypertension, signs of uremia). Many patients, however, are asymptomatic and are noted during routine examination to have an elevated serum creatinine concentration, or an abnormal urinalysis.

Once kidney disease is discovered, the presence or degree of kidney dysfunction and rapidity of progression are assessed, and the underlying disorder is diagnosed. Although the history and physical examination can be helpful, the most useful information is initially obtained from estimation of the GFR and examination of the urinary sediment.

Estimation of the GFR is used clinically to assess the degree of kidney impairment and to follow the course of the disease. However, the GFR provides no information on the cause of the kidney disease. This is achieved by the urinalysis, measurement of urinary protein excretion, and, if necessary, radiologic studies and/or kidney biopsy.

2.2 Laboratory measurement for diagnosis of CKD
2.2.1 For all patients at increased risk for CKD

- Serum creatinine to estimate GFR;
- Albumin-to-creatinine or protein-to-creatinine ratio in a first-morning or random untimed 'spot' urine specimen;
- Examination of the urine sediment or dipstick for red bloodcells and white blood cells.

2.2.2 For patients found to have CKD

- Imaging of the kidneys, usually by ultrasound;
- Serum electrolytes (sodium, potassium, chloride and bicarbonate)

2.2.3 Estimation of GFR

Once kidney disease is discovered, the presence or degree of kidney dysfunction and rapidity of progression are assessed, and the underlying disorder is diagnosed. Early identification of patients with CKD would allow treatment that could slow the progression to ESRD, improve clinical outcomes, and constrain the growth of costs in the ESRD program. Although the history and physical examination can be helpful, the most useful information is initially obtained from estimation of the GFR and examination of the urinary sediment.

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The GFR is equal to the sum of the filtration rates in all of the functioning nephrons, thus, estimation of the GFR gives an approximate measure of the number of functioning nephrons. GFR cannot be measured directly. Instead it is measured as the urinary clearance of an ideal filtration marker.

The most reliable assessment of GFR is based on the measurement of kidney clearance of a filtration marker such as Inulin which is a physiologically inert substance that is freely filtered at the glomerulus, and is neither secreted, reabsorbed, synthesized, nor metabolized by the kidney (Rahn et al., 1999). Thus, the amount of inulin filtered at the glomerulus is equal to the amount excreted in the urine, which can be measured. Inulin, however, is in short supply, expensive, and difficult to assay and is not suitable for routine clinical practice, and is cumbersome even for clinical research. Furthermore, the classic protocol for measuring inulin clearance requires a continuous intravenous infusion, multiple blood samples, and bladder catheterization.

Various less cumbersome methods for measuring clearance are available: using alternative filtration markers (such as radioactive or non-radioactive iothalamate, iohexol, DTPA, or EDTA), bolus administration of the marker (subcutaneous or intravenous), spontaneous bladder emptying, and plasma clearance (Rahn et al., 1999; Levey, 1990; Brandstrom et al., 1998). While these methods are simpler, all have disadvantages that limit their application in clinical practice and affect the interpretation of research studies.

In the United States, the most common methods utilized to estimate the GFR are the serum creatinine concentration, the creatinine clearance, or estimation equations based upon the serum creatinine: such as the Cockcroft-Gault equation and Modification of Diet in Renal Disease (MDRD) Study equations.

The K/DOQI guidelines classified patients by CKD stage, which is defined in part by the estimated GFR (table 1). The GFR should be estimated from the MDRD and Cockcroft-Gault equations, which take into account the serum creatinine concentration, and some or all of the following variables: age, gender, race, and body size.

The Cockcroft-Gault formula estimates creatinine clearance in milliliters per minute, and the MDRD equation estimates GFR in milliliters per minute per 1.73 m^2, and this difference should be kept in mind when comparing their outputs. However, the estimation equations have not been validated, and may be less accurate, in some populations. These include individuals with high, normal, or near-normal renal function, children, certain ethnic groups, pregnant women, and those with unusual muscle mass, body habitus, and weight (eg, morbid obesity or malnourished). Some, therefore, recommend measuring the creatinine clearance to estimate the GFR in these patients with stable renal function. Most patients with CKD stages 3 to 5 progress relentlessly to ESRD. A straight-line relationship is often found between the reciprocal of serum creatinine (1/SCr) values or the estimated GFR and time. The rate of progression of CKD varies according to the underlying nephropathy and how the kidney responds to injury.

Because of the problems with changes in creatinine production and secretion, other endogenous compounds have been evaluated in an effort to provide a more accurate estimation of GFR including symmetric dimethylarginine (Kielstein et al., 2006) and cystatin C. Perhaps the best studied and most promising is cystatin C, a low molecular weight protein, that is a member of the cystatin superfamily of cysteine protease inhibitors. Cystatin C is filtered at the glomerulus and not reabsorbed. However, it is metabolized in the tubules, which prevents use of cystatin C to directly measure clearance.

Cystatin C is thought to be produced by all nucleated cells; its rate of production has been thought to be relatively constant, and not affected by changes in diet, although this is not proven. Cystatin C has been purported to be unaffected by gender, age or muscle mass. However, higher cystatin C levels have now been associated with male gender, greater height and weight, and higher lean body mass (Knight et al., 2004; Groesbeck et al., 2008;

Macdonald et al., 2006). Cystatin C levels increase sharply with age (Knight et al., 2004). Analysis of a sub-sample of 7596 participants drawn from National Health and Nutrition Examination Survey III (NHANES III) revealed that more than 50 percent of individuals over age 80 have an elevated cystatin C level, and non-Hispanic whites and males have higher levels of cystatin C (Kottgen et al., 2008). These data were not adjusted for GFR; therefore, it is unclear whether they are related to different levels of kidney function among the populations, or difference in the non-GFR determinants of cystatin C. In addition, cystatin is affected by hyper- and hypothyroidism, and has been correlated with markers of inflammation (C-reactive protein), body size (in particular fat mass), and diabetes (Manetti et al., 2005; Stevens et al., 2009). Together, these data suggest that levels of cystatin C are affected by factors other than GFR.

Although reference ranges have been reported, there is no current standard for serum cystatin C measurements (Shlipak et al., 2005; Mussap & Plebani, 2004). In addition, testing for cystatin C is only available in a limited number of laboratories.

The serum cystatin C concentration may correlate more closely with the GFR than the serum creatinine concentration (Newman et al., 1995; Coll et al., 2000; Fliser & Ritz, 2001; Mussap et al., 2002; Ahlstrom et al., 2004; Hoek et al., 2003; Dharnidharka et al., 2002; Poge et al., 2006; Stevens et al., 2008). In multiple studies, serum cystatin C was more sensitive in identifying mild reductions in kidney function than serum creatinine (Coll et al., 2000; Hoek et al., 2003; Dharnidharka et al., 2002). Using the clearance of radioactive iothalamate as the gold standard, serum cystatin C levels began increasing at GFR levels of approximately 90 mL/min per 1.73 m^2, while the serum creatinine only increased when the GFR was approximately 70 mL/min per 1.73 m^2. Whether cystatin C correlates better with GFR than serum creatinine in patients with diabetic nephropathy is unclear (Oddoze et al., 2001; Perkins et al., 2005).

Estimation equations based on serum cystatin C have also been formulated (Grubb et al., 2005; Sjostrom et al., 2005; Grubb et al., 2005). It has been proposed that cystatin C-based equations would be more accurate in populations with lower creatinine production, such as the elderly, children, renal transplant recipients, or patients with cirrhosis (White et al., 2005; Poge et al., 2006). In one study of over 3000 patients with known CKD, an equation for the estimated GFR based upon cystatin C was nearly as accurate as GFR estimated from the serum creatinine adjusted for age, sex, and race when compared to GFR measured by iothalamate clearance (Stevens et al., 2008). The addition of age, sex and race to cystatin C reduced bias in some subgroups defined by these variables, and an equation that uses both serum creatinine and cystatin C with age, sex and race was better than equations that used only one of these markers.

Steroid use may affect cystatin C levels, therefore, limiting its use in transplant recipients. As an example, for the same level of cystatin C, measured GFR was 19 percent higher in transplant recipients than in patients with native kidney disease.

Although cystatin C appears to be more accurate for the assessment of GFR than serum creatinine in certain populations, whether measurement of cystatin C levels will improve patient care is at present unknown [Deinum & Derkx, 2000].

2.3 Markers of kidney damage

Markers of kidney damage include proteinuria, hematuria, and other abnormalities of the urinary sediment, and radiologic evidence of damage. The most common cause of CKD in adults are diabetes and hypertension, and, therefore, the most common marker for kidney damage is increased excretion of protein, and specifically of albumin. Measurement of

protein excretion is useful in a variety of clinical settings, particularly to establish the diagnosis and to follow the course of glomerular disease.

In normal subjects, low molecular weight proteins and small amounts of albumin are filtered. The actual amount of albumin filtered each day in humans is controversial. The majority view is that no more than about 2 to 4 g of albumin per day are filtered normally, but some investigators claim that as much as 200 g of albumin are filtered each day (with the bulk of this filtered albumin "reclaimed" in the early proximal tubule) (Russo et al., 2007). The filtered proteins enter the proximal tubule where they are almost completely reabsorbed and then catabolized by the proximal tubular cells. Some of the catabolized proteins (including albumin) are excreted as peptides in the urine. These are not detected by dipstick or the immuno-nephelometric albumin-specific assays, but are detected by chromatographic assays. The net result is the normal daily protein excretion of less than 150 mg (usually 40 to 80 mg), of which approximately about 4 to 7 mg is intact, immuno-reactive albumin.

Previously, abnormal proteinuria was generally defined as the excretion of more than 150 mg of protein per day. However, it is now clear that early renal disease is reflected by lesser degrees of proteinuria, particularly increased amounts of albuminuria.

The normal rate of albumin excretion is less than 20 mg/day (15 µg/min); the rate is about 4 to 7 mg/day in healthy young adults and increases with age and with an increase in body weight. Persistent albumin excretion between 30 and 300 mg/day (20 to 200 µg/min) is called microalbuminuria. In patients with diabetes, this is usually indicative of incipient diabetic nephropathy (unless there is some co-existent renal disease). In non-diabetics, the presence of microalbuminuria is associated with cardiovascular disease.Values above 300 mg/day (200 µg/min) are considered to represent overt proteinuria or macroalbuminuria, the level at which the standard dipstick becomes positive. At this level, practically all protein in the urine consists of albumin.

The standard urinary dipstick measures albumin concentration via a colorimetric reaction between albumin and tetrabromophenol blue producing different shades of green according to the concentration of albumin in the sample

- Negative
- Trace — between 15 and 30 mg/dl
- 1+ — between 30 and 100 mg/dl
- 2+ — between 100 and 300 mg/dl
- 3+ — between 300 and 1000 mg/dl
- 4+ — >1000 mg/dl

The urine dipstick is, therefore, not very accurate in assessing the severity of proteinuria since the protein concentration is a function of urine volume as well as the quantity of protein present. As an example, suppose a patient excretes 500 mg of protein per day. If the urine volume is two liters, the protein concentration will be 25 mg/dl, resulting in a trace to 1+ findings on the dipstick. However, if the urine volume is only 500 ml, the protein concentration will be 100 mg/dl and the dipstick will read 2+.

The urine dipstick is also a relatively insensitive marker for initial increases in protein excretion, not generally becoming positive until protein excretion exceeds 300 to 500 mg/day. Limited data suggest that the combination of specific gravity plus dipstick proteinuria may significantly improve the ability to detect proteinuria (Constantiner et al., 2005).

The dipstick may also be insufficiently sensitive in multiple myeloma. Given that the dipstick primarily detects urinary albumin, it may be negative in patients with multiple myeloma who

may excrete relatively large amounts of monoclonal immunoglobulin light chains. In contrast, testing the urine with sulfosalicylic acid will detect all proteins, as evidenced by the degree of turbidity (Rose, 1987). As a result, any patient with unexplained renal failure, a benign urine sediment, and a negative dipstick for protein should have the urine tested with sulfosalicylic acid. A positive finding suggests the presence of non-albumin proteins in the urine, which in adults usually represents immunoglobulin light chains.

The accurate measurement of protein excretion in the urine can be performed by several different techniques. The gold standard for measurement of protein excretion is a 24 hour urine collection, with the normal value being less than 150 mg/day. However, an adequate collection must be ensured. This is cumbersome for patients and physicians; thus, measurement on random specimens has become an accepted alternative method.

The preferred method of measuring urinary protein excretion in patients with proteinuria is either the total protein-to-creatinine ratio or albumin-to-creatinine ratio for microalbuminuria on a random urine specimen (Eknoyan et al., 2003; KDOQI, 2002).

These ratios on a random urine specimen correlate fairly closely with daily protein excretion in g/1.73 m² of body surface area (Ginsberg et al., 1983; Schwab et al., 1987; Abitbol et al., 1990; Steinhauslin & Wauters, 1995; Chitalia et al., 2001; Zelmanovitz et al., 1997; Bakker, 1999). Thus, a ratio of 4.9 (as with respective urinary protein and creatinine concentrations of 210 and 43 mg/dl) represents daily protein excretion of approximately 4.9 g/1.73 m².

The accuracy of the ratio is diminished when creatinine excretion is either markedly increased in a muscular man (the ratio will underestimate proteinuria) or markedly reduced in a cachectic patient (the ratio will overestimate proteinuria).

Because of this markedly increased convenience, the total protein-to-creatinine ratio or albumin-to-creatinine ratio are preferred to the 24 hour urine collection for quantitative measurement of significant urinary protein. First morning specimens are preferred, but random daytime specimens are acceptable if first morning specimens are not available (Witte et al., 2009). Specimens obtained in the evening or overnight appear to be least accurate.

The range of the urinary albumin-to-creatinine ratio with microalbuminuria varies by gender, being 20 to 200 mg/g and 30 to 300 mg/g for males and females, respectively. This is a result of the higher muscle mass observed in males.

Hematuria or pyuria originating in the renal parenchyma, glycosuria in the absence of hyperglycemia, and abnormal radiologic or pathologic studies are others diagnostic criteria for CKD.

3. Natural history of CKD

The kidney is able to adapt to damage by increasing the filtration rate in the remaining normal nephrons, a process called adaptive hyperfiltration. As a result, the patient with mild renal insufficiency often has a normal or near-normal serum creatinine concentration. Additional homeostatic mechanisms (most frequently occurring within the renal tubules) permit the serum concentrations of sodium, potassium, calcium, and phosphorous and the total body water to also remain within the normal range, particularly among those with mild to moderate renal failure. Adaptive hyperfiltration, although initially beneficial, appears to result in long-term damage to the glomeruli of the remaining nephrons, which is manifested by proteinuria and progressive renal insufficiency. This process appears to be responsible for the development of renal failure among those in whom the original illness is

either inactive or cured (Abboud & Henrich, 2010). The institution of measures to help prevent this process, such as antihypertensive therapy with an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker, may slow progressive disease and even preserve renal function. If these modalities are effective, the benefit is likely to be greatest if begun before a great deal of irreversible scarring has occurred.

Not all individuals have progressive loss of kidney function. Some studies show a high rate of progression, while others report relatively stable disease (Sarnak et al., 2005; Eriksen & Ingebretsen, 2006; Hallan et al., 2006). The rate of progression of CKD from one major stage to another varies based upon the underlying disease, presence or absence of comorbid conditions, treatments, socioeconomic status, individual genetics, ethnicity, and other factors.

Using epidemiologic data, general estimates for the rate of transition from a GFR between 15 to 60 ml/min per 1.73 m^2 to end stage disease may be approximately 1.5 percent per year, while the rate of transition from a GFR above 60 to below 60 ml/min per 1.73 m^2 may be approximately 0.5 percent per year (Hsu et al., 2004; Fox et al., 2004).

Historically, rate of decline in GFR of patients with diabetic nephropathy (DN) has been among the fastest, averaging about 10 ml/min/year. Control of systemic hypertension slows the rate of GFR decline to 5ml/min/year. In non-diabetic nephropathy, the rate of progression of CKD was 2.5 times faster in patients with chronic glumerulonephritis than in those with chronic interstitial nephritis, and 1.5 times faster than in those with hypertensive nephrosclerosis. Polycystic kidney disease (PKD) and impaired renal function may also have a faster rate of progression compared to those with other nephropathies.

4. Prevalence of chronic kidney disease

The prevalence of CKD has been evaluated based on serum creatinine concentrations and microalbuminuria in the following population studies from the United States, as well as some other countries.

In the Third National Health and Nutrition Examination Survey (NHANES III), serum creatinine concentration was obtained in a sample of 18,723 individuals aged 12 years and older between 1988 and 1994 (Jones et al., 1998). The prevalence of a serum creatinine level at or above 1.5, 1.7, and 2.0 mg/dl was 5.0, 1.9, and 0.6 percent for men, respectively, and 1.6, 0.7, and 0.3 percent for women.

By extrapolating the results of the NHANES III to the 1990 US Census population, it was estimated that the number of people with serum creatinine at or above 1.5, 1.7, and 2.0 mg/dl is 6.2, 2.5, and 0.8 million, respectively. It should be noted, however, that only a single creatinine measurement per patient was used to estimate the prevalence of CKD, and that serum creatinine was available in only 31 percent of the potentially eligible sample.

In a study of nearly 200,000 patients enrolled in a large health maintenance organization (HMO) in the southwestern US in 1997, the prevalence of at least one gender specific elevated serum creatinine (>1.2 mg/dl in women and >1.4 mg/dl in men) was 3.7 percent, and of at least two elevated serum creatinine levels separated by at least 90 days was 1.7 percent (Nissenson et al., 2001).

The prevalence estimates from this HMO study, as applied to United States Census data, led to the estimate of 9.1 million Americans in 1990 who had at least one elevated serum creatinine concentration, and 4.2 million Americans who had at least two elevated creatinine values separated by 90 days or greater.

The prevalence of CKD in Norway was estimated from a population-based health survey of Nord-Trondelag County (HUNT II), which included 65,181 adults in 1995 through 1997 (participation rate 70.4%) (Erikson & Ingebretsen, 2006). The primary analysis used gender-specific cutoffs in estimating persistent albuminuria for CKD stages 1 and 2. Total CKD prevalence in Norway was 10.2% (SE 0.5): CKD stage 1 (GFR>90 ml/min per 1.73 m^2 and albuminuria), 2.7% (SE 0.3); stage 2 (GFR 60 89 ml/min per 1.73 m^2 and albuminuria), 3.2% (SE 0.4); stage 3 (GFR 30 to 59 ml/min per 1.73 m^2, 4.2% (SE 0.1); and stage 4 (GFR 15 to 29 ml/min per 1.73 m^2, 0.2% (SE 0.01).

Forty two percent of men and 44 percent of women over the age of 85 had an MDRD-estimated GFR less than 60 ml/min per 1.73 m^2 in the Nijmegen Biomedical Study, a population-based cross-sectional study conducted in the eastern part of the Netherlands. In a report from Taiwan, the prevalence of an estimated GFR <60 ml/min per 1.73 m^2 was 7 % (Hsu et al., 2006).

In a population-based survey from Pakistan, Kazmi et al have reported the prevalence of CKD stages 3 and 4 to be about 21 million (Kazmi et al., 2007).

Stage	Description	GFR (ml/min/1.73m²)
1	Kidney damage with normal GFR	90 or more
2	Mildly deceased GFR	60 - 89
3	Moderately decreased GFR	30 - 59
4	Severely decreased GFR	15 - 29
5	Advanced kidney failure requiring dialysis/kidney transplant	< 15

Table 1. National Kidney Foundation K/DOQI Classification of Chronic Kidney Disease based on GFR levels.

5. Screening for chronic kidney disease

The NKF-K/DOQI guidelines for CKD, which have been reviewed and endorsed by the 2006 Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference, recommend that all individuals should be assessed as part of routine health examinations to determine whether they are at increased risk for developing CKD (KDOQI, 2002).

Some data suggest, however, that screening the general population may decrease the incidence of ESRD resulting from glomerulonephritis. However, screening the general population is unlikely to be cost-effective. Screening for CKD among select patients who are at risk for development of CKD is justified because therapeutic interventions may slow or prevent the progression toward ESRD. Such patients include those with a history of diabetes, cardiovascular disease, hypertension, hyperlipidemia, obesity, metabolic syndrome, smoking, HIV or hepatitis C virus infection, and malignancy. A family history of CKD, age >60 years and treatment with potentially nephrotoxic drugs should also prompt screening for CKD. Testing for CKD can be done with a urinalysis, a first morning or a random "spot" urine sample for albumin or protein and creatinine assessment, and a serum creatinine level. Depending upon the presence of particular risk factors, additional testing

such as renal ultrasonography may be required, such as in patients with a family history of polycystic kidney disease. Once the diagnosis is established and the cause and/or potentially reversible factors are identified and treated, CKD should be staged according to the classification proposed by the NKF-K/DOQI.

6. Mechanisms of progression of chronic kidney disease

Regardless of the nature of the underlying nephropathy, the progression of CKD is associated with the progressive sclerosis of glomeruli, tubulointerstitial fibrosis, and vascular sclerosis which can be initiated by endothelial, mesangial, or epithelial cell injury or damage. The kidney responds to injury by adaptive changes that lead to remodeling evolving towards either healing and functional recovery or scarring with loss of kidney function and progressive CKD. Healing is characterized by recovery of kidney function and structure. It occurs primarily in AKI when acutely damaged tubules recover from the initial insult and replace lost tubular cells to reconstitute the integrity of the tubules and to restore kidney function.

On the other hand, most forms of chronic kidney damage, such as those induced by diabetes, hypertension, chronic glomerulonephritis, or chronic exposure to infections, evolve to progressive scarring with loss of function and CKD. Scarring is characterized by progressive loss of intrinsic renal cells and their replacement by fibrous tissue made of collagenous extracellular matrix.

Within glomerular capillaries, endothelial cells are the first to be exposed to damage induced by hemodynamic, immunologic, or metabolic insults. Glomerular endothelial injury is associated with reduction or loss of their physiologic anticoagulant and anti-inflammatory properties and the acquisition of procoagulant and inflammatory characteristics.

Glomerular endothelial injury can induce proliferation, phenotype change (expression of adhesion molecules), release of vasoactive agents (endothelin, nitric oxide), infiltration of glomerular tufts by inflammatory cells and conversion to a prothrombotic state. Glomerular endothelial injury is characterized by proliferation, apoptosis, detachment, and (particularly) thrombosis.

Mesangial cells are the glomerular capillary equivalent to the smooth muscle cells and in that capacity respond to injury in a similar fashion; death, transformation, proliferation, and migration as well as synthesis and deposition of extracellular matrix.

The mesangial response to injury is characterized by alterations in cell cycle proteins that favor cell proliferation, phenotype change (to an actin positive myofibroblast), extracellular matrix production, and apoptosis. Many of these effects involve agonist interaction with specific receptors on the mesangial cell, including receptors for IgA, toll-like receptors, and transferrin receptors. Platelet derived growth factor (PDGF) appears to be the principal mediator of mesangial cell migration and proliferation in glomerular disease, an effect possibly magnified in hypoxic conditions. Receptors for PDGF are also upregulated. Further support for a role for PDGF is provided by a study that demonstrated prevention of renal scarring by antagonism of PDGF in an animal model of glomerulonephritis.

Mesangial cell proliferation is associated with the increased expression of cyclin-dependent kinases and reduced expression of cyclin kinase inhibitors, such as P21 and P27. Mesangial cell proliferation is an essential precursor to subsequent mesangial matrix expansion and

sclerosis, due primarily to the actions of TGF and CTGF. Increased prostanoid synthesis, possibly modulated by TGF, may also have a role in this process. Therapeutic interventions, which target mesangial cell proliferation or matrix production, can therefore greatly ameliorate both acute and chronic forms of glomerular injury in those disorders in which glomerular cell proliferation is prominent.

The relative inability of podocytes to replicate in response to injury may lead to their stretching along the GBM, expressing areas of denuded Glomerular basement membrane (GBM) that would attract and interact with parietal epithelial cells leading to the formation of capsular adhesions and subsequent segmental glomerulosclerosis. This may lead to the accumulation of amorphous material in the paraglomerular space and the subsequent disruption of glomerular-tubular junction resulting in atubular glomeruli.

6.1 Extrinsic cells

Neutrophils: Neutrophils are present in the early biopsies of patients with post-streptococcal glomerulonephritis (GN), membranoproliferative GN, Henoch-Schönlein purpura (HSP), systemic lupus erythematosus (SLE), and some forms of rapidly progressive glomerulonephritis (RPGN) [Ishida-Okawara et al., 2004; Tipping & Holdsworth, 2003].

Neutrophil localization in glomerular capillaries is dependent upon the generation of chemotactic factors within and around an inflammatory focus; the most prominent chemo-attractants in glomerular disease are C5a (derived from activation of complement) and several chemokines, such as interleukin-8, which can be bound to endothelial cells via heparan sulfate proteoglycans (Segerer et al., 2000; De Vriese et al., 1999; Kitching et al., 2002; Rops et al., 2004; Johnson et al., 2001; Segerer & Schlondorff, 2007).

Once attracted, neutrophil localization involves the interaction between adhesion molecules expressed on glomerular endothelial cells, such as selectins, integrins (CD11/CD18), and Ig-like molecules (ICAM-1), and their corresponding ligands on the neutrophil (Segerer et al., 2000; De Vriese et al., 1999; Johnson et al., 2001; Ito et al., 2001).

At the site of immune deposit formation, neutrophils phagocytose the immune complex aggregates, become activated and undergo a respiratory burst that generates reactive oxygen species (Johnson et al., 1987). Several studies have shown hydrogen peroxide to be the principal neutrophil-derived oxidant that mediates glomerular injury. Hydrogen peroxide is nephritogenic because of interactions with another neutrophil-derived cationic enzyme myeloperoxidase (MPO) (which also localizes in glomeruli because of charge) and a halide to form hypohalous acids, which halogenate the glomerular capillary wall (Johnson et al., 1987; Johnson et al., 2001).

Neutrophils also store cationic serine proteases, such as elastase and cathepsin G, within azurophilic granules. The activation of neutrophils within glomeruli causes the extracellular release of these proteins, thereby resulting in the degradation of elements of the glomerular capillary wall. MPO and PR3, both cationic proteases localized in the primary granules of neutrophils, are also involved in the pathogenesis of ANCA-positive crescentic glomerulonephritis; they are localized in primary granules and displayed on the cell surface in response to certain cytokines. There they are accessible to ANCA antibody and become activated, resulting in capillary localization and release of oxidants and proteases (Xiao et al., 2005). Evidence in animal models suggests that ANCA-neutrophil interaction also induces release of a complement-activating factor that contributes to the mediation of injury (Huugen et al., 2007; Jennete & Falk, 2008).

Macrophages: Macrophages are also prominent constituents of several glomerular lesions, particularly ones that exhibit crescent formation such as RPGN, SLE, and cryoglobulinemic nephropathy (Hooke et al., 1987; Rastaldi et al., 2000; Kurts et al., 2007). The importance of monocytes/macrophages in mediating glomerular injury is well-documented by studies, such as macrophage depletion and inhibition of macrophage inhibitory factor (MIF) (Kurts et al., 2007). The protective effect of absent granulocyte macrophage colony stimulating factor is illustrated in GM-CSF -/- mice, which exhibited less infiltration of monocytes compared to wild type and were protected from crescentic glomerular injury (Timoshanko et al., 2005).

Macrophages localize to glomeruli via interactions with both deposited immunoglobulins (through Fc receptors) and several chemokines, such as macrophage chemo-attractant protein-1 (MCP-1) and macrophage inflammatory protein-1-alpha (MIP-1alpha) and RANTES (Timoshanko et al., 2005; Shimizu et al., 2003). Unlike neutrophils, macrophages are also readily recruited by lymphocyte-derived molecules, such as MIF, that result from the interaction between specifically sensitized T-cells and intraglomerular antigens (Chitalia et al., 2001). In addition, monocytes also localize through interaction with leukocyte adhesion molecules, such as ICAM-1 and VCAM-1, as well as osteopontin (Kurts et al., 2007; Okada et al., 2000).

Thus, macrophages may serve as effector cells in both humoral and cell-mediated forms of immune injury and are presumed to be the principal effector cells in inflammatory glomerular lesions induced by sensitized T-cells in the absence of antibody (Kurts et al., 2007). As with neutrophils, macrophages may generate oxidants and proteases. However, unlike neutrophils, they release tissue factor (which initiates fibrin deposition and crescent formation) and TGF beta (which contributes to the synthesis of extracellular matrix and eventual development of sclerosis).

T cells: T cells are rarely conspicuous in glomerular lesions, but can be detected, particularly in diseases primarily mediated by macrophages such as crescentic GN (Tipping & Holdsworth, 2003; Hooke et al., 1987; Kurts et al., 2007). Although there is experimental evidence that glomerular injury can be induced by systemic T-cells in the absence of antibody deposition, little evidence exists that glomerular T-cells alone are nephritogenic, with the exception of permeability factors (Renneke et al., 1994). Instead, T-cell mediated injury occurs primarily via the release of chemokines and recruitment of macrophages, which subsequently function as effector cells. In addition, T cells may be the source of permeability factors that contribute to non-inflammatory glomerular injury (Kurts et al., 2007).

Platelets: Platelets are prominent in several glomerular lesions, usually ones that involve intraglomerular thrombosis such as SLE, anti-phospholipid antibody syndromes, and thrombotic microangiopathies. In addition to their role in thrombotic processes involving endothelial cell injury, platelets also release a number of products that participate in and augment glomerular injury, more broadly including vasoactive, mitogenic, and chemotactic substances (Barnes, 2001). For example, platelet-derived factors such as PAF and platelet factor 4 enhance glomerular permeability to proteins and immune complex deposition, and PDGF and TGF contribute to mesangial cell proliferation and sclerosis, respectively. Platelets have also been shown to contribute to neutrophil-mediated glomerular injury through non-chemotactic mechanisms.

6.2 Tubulo-interstitial disease (fibrosis)

All forms of CKD are associated with marked tubulointerstitial injury (tubular dilatation, interstitial fibrosis), even if the primary process is a glomerulopathy (Ong & Fine, 1994;

Nath, 1982). Furthermore, the degree of tubulo-interstitial disease is a better predictor of the GFR and long-term prognosis than is the severity of glomerular damage in almost all chronic progressive glomerular diseases, including IgA nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis, and lupus nephritis (Nath, 1982; D'Amico, 1992; Alexopoulos et al., 1990; Bajema et al., 1999; Bazzi et al., 2002; Meyer, 2003). It is possible in these settings that tubulointerstitial disease causes tubular atrophy and/or obstruction, eventually leading to nephron loss.

The mechanism by which tubulointerstitial fibrosis develops is incompletely understood [Alexopoulos et al., 1990; Lan et al., 1991; Eddy, 1994; Nath, 1998). Infiltration of the kidney by macrophage and T lymphocytes (and perhaps bone marrow derived fibroblast-like cells), resulting in the subsequent production of transforming growth factor beta (TGF-beta) and other profibrotic factors, may be central to the development of this process (Lan et al., 1991).

Other possible contributors include calcium phosphate deposition, and metabolic acidosis with secondary interstitial ammonia accumulation.

6.3 Angiotensin II

Non-hemodynamic effects of angiotensin II also appear to contribute to the development of tubulointerstitial fibrosis, mediated via one of the angiotensin II type 1 receptors that are present in the glomerulus (Ruiz-Ortega et al., 2006). Animal studies have suggested that activation of angiotensin II receptor type 1B, which is largely limited to the glomerulus, but not type 1A, may accelerate renal injury (Crowly et al., 2009). This effect is likely due to the generation of profibrotic factors such as TGF-beta, connective tissue growth factor, epidermal growth factor, and other chemokines (Aros & Remuzzi, 2002). Further support for this role is provided by the finding that the expression of angiotensin II type 1 receptors in podocytes is associated with focal segmental glomerulosclerosis (Hoffmann et al., 2004). It also appears that renin may lead to a receptor-mediated increase in TGF-beta that is independent of angiotensin II (Huang et al., 2006).

Actions of angiotensin II may also be mediated via epidermal growth factor (EGF) receptors, which are present throughout the nephron, and when stimulated, promote cell proliferation and collagen production via transforming growth factor-alpha (TGF-alpha), EGF, and other growth factors (Lautrette et al., 2005; Chen et al., 2006). In experimental models, infusion of angiotensin II induces glomerulosclerosis and tubular atrophy. This effect is not seen in mice lacking EGF receptors or TGF-alpha, and pharmacologic inhibition of angiotensin II prevented these renal lesions. Angiotensin II also participates in cytokine- and chemokine-mediated recruitment of inflammatory cells into the kidney.

6.4 Vascular sclerosis

Vascular sclerosis is an integral feature of the renal scarring process. Renal arteriolar hyalinosis is present in CKD at an early stage, even in the absence of severe hypertension. Vascular sclerosis is associated with progressive renal failure in glomerulonephritis. Hyalinosis of afferent arterioles has been implicated in the pathogenesis of diabetic glomerulosclerosis. Changes in postglomerular arterioles and damage to peritubular capillaries may further exacerbate interstitial ischemia and fibrosis. Ischemia and the ensuing hypoxia are fibrogenic influences that stimulate tubular cells and renal fibroblast to produce ECM components and reduce their collagenolytic activity.

7. Factors affecting progression of chronic kidney disease

A variety of chronic kidney diseases progress to ESRD, including chronic glomerulonephritis, diabetic nephropathy, and polycystic kidney disease. Although the underlying problem often cannot be treated, extensive studies in experimental animals and humans suggest that progression in CKD may be largely due to secondary factors that are sometimes unrelated to the activity of the initial disease. These include systemic and intraglomerular hypertension, glomerular hypertrophy, the intrarenal precipitation of calcium phosphate, hyperlipidemia, and altered prostanoid metabolism (tables 2, 3). (Jacobson, 1991; Renneke et al., 1989; Loghman-Adham, 1993; Nagata & Kriz, 1942; Yu, 2003).

7.1 Genetic factors

A number of genetic factors (eg, single nucleotide polymorphisms and modifier genes) may influence the immune response, inflammation, fibrosis, and atherosclerosis, possibly contributing to accelerated progression of CKD (Nordfors et al., 2005; Hsu et al., 2006). Indirect evidence in support of such factors can be found in familial clustering of all-cause ESRD, with approximately one-quarter of dialysis patients having relatives with ESRD (Freedman et al., 2005). This is consistent with the hypothesis that common kidney diseases and progression to ESRD are influenced by the inheritance of specific genes. Genetic studies have suggested possible links between CKD and a variety of alterations or polymorphisms of genes coding for putative mediators including the renin angiotensin system, nitric oxide synthase, kallikrein, growth factors including platelet-derived growth factors and cytokines.

With respect to specific genes, apolipoprotein E (ApoE) polymorphisms may alter the risk of atherosclerotic disease, and, therefore, progression of CKD. The ApoE epsilon-2 allele is associated with elevated lipoprotein and triglyceride levels, whereas the ApoE epsilon-4 allele is associated with elevated levels of high density lipoprotein and lower triglycerides. In a secondary analysis of the Atherosclerosis Risk in Communities Study of 14, 520 patients with a median follow-up of 14 years, individuals with an ApoE epsilon-4 allele (present in 30 percent) had a 15 percent reduction in risk of progression of CKD compared to individuals with ApoE epsilon-3 allele (present in 90 percent) (Hsu et al., 2005). The risk with the ApoE epsilon-2 allele was not significantly different compared with ApoE epsilon-3**.**

Risk factors	Definition
Susceptibility factors	Factors predisposing to CKD include genetic and familial predisposition, race, maternal-fetal factors (low birth weight, malnutrition in utero), age (elderly), gender (male)
Initiation factors	Factors directly trigger kidney damage include diabetes, hypertension, cardiovascular disease, dyslipidemia, obesity, hyperuricemia and nephrotoxin exposure
Progression factors	Factors associated with worsening of already established kidney damage include poor glycemia control, poor blood pressure control, cardiovascular disease, proteinuria, alcohol consumption, nephrotoxin exposure, and acute kidney injury

Table 2. Types of risk factors for chronic kidney disease and its outcomes.

Intraglomerular hypertension and hypertrophy
Phosphate retention, with interstitial CaPO4 deposition
Increased prostaglandin synthesis
Hyperlipidemia, especially in the nephrotic syndrome
Metabolic acidosis
Obesity
Smoking
Type of underlying kidney disease
Proteinuria
Tubulointerstitial disease
Retained "uremic" toxins
Filtered iron in nephrotic syndrome

Table 3. Secondary factors and progression of CKD.

7.2 Hypertension

Systemic hypertension is both a cause and consequence of CKD. The incidence of hypertension increases as CKD advances. The prevalence of hypertension requiring treatment in patients with stage 4 CKD is greater than 80%. There is strong evidence that high blood pressure is a risk factor for the progression of CKD in humans. It is believed that the transmission of systemic hypersion into the glomerular capillary beds and the resulting glomerular hypertension contribute to the initiation of glomerulosclerosis and, there is clear evidence that strict control of the blood pressure is beneficial in slowing the rate of progression of CKD.

7.3 Proteinuria

Proteinuria alone may contribute to disease progression (Burton & Harris, 1996; Eddy et al., 1991; Benigini et al., 2004; Hirschberg & Wang, 2005). Proposed mechanisms include mesangial toxicity, tubular overload and hyperplasia, toxicity from specific filtered compounds such as transferrin/iron and albumin-bound fatty acids, and induction of proinflammatory molecules such as MCP-1 and inflammatory cytokines (Wang et al., 1997).

It is possible, for example, that a marked increase in protein filtration and subsequent proximal reabsorption leads to tubular cell injury and the release of lysozymes into the interstitium. To the degree that proteinuria alone might be important, reversing intraglomerular hypertension with protein restriction or antihypertensive therapy may be beneficial both by diminishing hemodynamic injury to the glomeruli and by reducing protein filtration (which is in part dependent upon the intraglomerular pressure), thereby lowering proteinuria.

7.4 Hyperlipidemia

Hyperlipidemia is common in patients with CKD, particularly those with the nephrotic syndrome. In addition to accelerating the development of systemic atherosclerosis, experimental studies suggest that high lipid levels also may promote progression of the renal disease (Keane, 1994; Grone & Grone, 2008). The major experimental evidence in support of this hypothesis are the observations in experimental animals that cholesterol loading enhances glomerular injury and that reducing lipid levels with a drug such as lovastatin slows the rate of progressive injury (Keane, 1994; Diamond & Karnovsky, 1987;

Rubin et al., 1994; Michel et al., 1997). Furthermore, the beneficial effect of lipid lowering may be additive to that of lowering the blood pressure in at least some models of CKD (Rubin et al., 1994).

The factors responsible for the lipid effects are incompletely understood. In different animal models, a high cholesterol intake may be deleterious in association with a rise in intraglomerular pressure (Diamond & Karnovsky, 1987), while lipid-lowering agents may be beneficial without affecting glomerular hemodynamics. These disparate observations suggest that mechanisms other than intraglomerular pressure alone may play a contributory role. It has been shown experimentally, for example, that hyperlipidemia activates the mesangial cells (which have LDL receptors), leading to stimulation of mesangial cell proliferation and to increased production of macrophage chemotactic factors, fibronectin (a component of the extracellular matrix), type IV collagen, plasminogen activator-1 and reactive oxygen species.

Each of these changes could contribute to glomerular injury. In addition, statins may act independent of plasma lipid levels by directly inhibiting mesangial cell proliferation and production of monocyte chemo-attractants.

The applicability of these findings to human disease is uncertain. There are numerous secondary analyses of data from lipid trials suggesting that high lipid levels are associated with a faster rate of progression, and that statins slow the rate of progression of kidney failure.

7.5 Hyperuricemia

Hyperuricemia can develop in patients with CKD due to decreased urinary excretion. It has been proposed that hyperuricemia may contribute to progression, in part by decreasing renal perfusion via stimulation of afferent arteriolar vascular smooth muscle cell proliferation (Ohno et al., 2001; Iseki et al., 2004; Sanchez-Lozada et al., 2005; Schwarz et al., 2006).

Combined data from two community-based cohorts comprising 13,388 individuals were examined for an association between baseline uric acid and the development of CKD during 9 years of follow-up. Baseline uric acid was associated with increased risk for CKD with odds ratios of 1.07 (95% CI 1.01 to 1.14) and 1.11 (95% CI 1.02 to 1.21) per 1 mg/dl increase in uric acid, in both GFR and serum creatinine based models.

In a Japanese study, hyperuricemic patients with IgA nephropathy had a worse prognosis than those with normal uric acid level, and a serum uric acid greater than 6mg/dl was an independent predictor of ESRD in women.

7.6 Phosphate retention

A tendency to phosphate retention is an early problem in kidney disease, beginning as soon as the GFR starts to fall. In addition to promoting bone disease, the excess phosphate also may contribute to progression of CKD. Higher serum phosphorus concentrations have been associated with a greater risk of progression. In an observational study of 985 patients followed for a median of two years, the adjusted hazard ratio for doubling of the serum creatinine was 1.3 for every 1.0 mg/dl [0.33 mmol/l] increase in serum phosphorus (Schwarz et al., 2006).

A similar relationship was noted for the calcium-phosphorus product.

A potential causative mechanism could be calcium phosphate precipitation in the renal interstitium (Gimenez et al., 1987), which might initiate an inflammatory reaction, resulting in interstitial fibrosis and tubular atrophy.

These observations do not prove a cause-and-effect relationship and there are no data addressing the possible role of improved calcium and phosphorus control in slowing the progression of CKD. However, there are other compelling reasons for optimizing phosphorus control in patients with CKD.

7.7 Type of underlying kidney disease
The type of kidney disease appears to be a risk factor. Glomerulonephritis, diabetic and hypertensive nephropathies, and polycystic kidney disease tend to progress faster than tubulointerstitial disease.

7.8 Metabolic acidosis and increased ammonium production
As the number of functioning nephrons declines, each remaining nephron excretes more acid (primarily as ammonium). The local accumulation of ammonia can directly activate complement, leading to secondary tubulointerstitial damage (at least in experimental animals) (Nath et al., 1985). On the other hand, buffering the acid with alkali therapy prevents the increase in ammonium production and minimizes the renal injury. Although the renal protective effect of alkali therapy is unproven in humans, there are other reasons (prevention of osteopenia and muscle wasting) why correction of the acidemia might be desirable.

7.9 Smoking
Cigarette smoking increases systemic blood pressure and affects renal hemodynamics. In diabetic and non-diabetic patients, smoking is associated with a faster rate of decline of CKD. In one study of men with CKD, smoking increased the risk for ESRD threefold in patients treated with ACE inhibitors; with the odds ratio increasing to 10 in those taking other antihypertensive agents.

8. Clinical manifestations of chronic kidney disease

A wide range of disorders may develop as a consequence of the loss of renal function. In the early phase, stage 1 and 2, the patient is asymptomatic, blood urea nitrogen (BUN) and serum creatinine (SCr) are normal or near-normal, and acid base, fluid, and electrolyte balances are maintained through an adaptive increase of function in the remaining nephrons. A reduction of GFR to 30 to 59 ml/min/1.73 m^2 define stage 3, moderate impairment of GFR. The patient usually has no symptoms, although SCr and BUN are increased, and serum levels of hormones such as erythropoietin, calcitriol, and parathyroid hormones (PTH) are usually abnormal. Stage 4, severe impairment of GFR, involves a further loss of kidney function. Finding, if present, are mild; patients may have anemia, acidosis, hypocalcemia, hyperphosphatemia and hyperkalemia. The final stage of kidney disease, stage 5 is defined by a GFR of less than 15ml/min/1.73 m^2, is usually characterized by worsening of all the aforementioned findings, and symptoms including fatigue, dysgeusia, anorexia, nausea, and pruritis may develop.

8.1 Hypertension
Hypertension is present in approximately 80 to 85 percent of patients with CKD [MMWR, 2007]. The prevalence of hypertension increases linearly as the GFR falls and, as in patients

without renal disease, is increased in patients with higher body weight and in blacks. Data from the Modification of Diet in Renal Disease Study, for example, showed that the prevalence of hypertension rose progressively from 65 to 95 percent as the GFR fell from 85 to 15 ml/min per 1.73 m² (Buckalew et al., 1996).

One or more of the following factors may contribute in the individual patient:

- Sodium retention is generally of primary importance, even though the degree of extracellular volume expansion may be insufficient to induce edema.
- Increased activity of the renin-angiotensin system (probably due to regional ischemia induced by scarring) is often responsible for at least part of the hypertension that persists after the restoration of normovolemia.
- Enhanced activity of the sympathetic nervous system has been demonstrated in patients with CKD. The afferent signal may arise in part within the failing kidneys, since it is not seen in patients who have undergone bilateral nephrectomy (Ligtenberg et al., 1999; Neumann et al., 2004).

Secondary hyperparathyroidism raises the intracellular calcium concentration, which can lead to vasoconstriction and hypertension (Raine et al., 1993). Lowering parathyroid hormone secretion by the chronic administration of an active vitamin D analog can reduce both intracellular calcium and the systemic blood pressure.

- Hypertension may occur or be exacerbated in patients with advanced CKD treated with erythropoietin; this effect is in part related to the degree of elevation in the hematocrit.
- Impaired nitric oxide synthesis and endothelium-mediated vasodilatation has been demonstrated in patients with uremia (Passauer et al., 2005; Passauer et al., 2005). Although the mechanisms are unclear, potential explanations include reduced nitric oxide availability due to a state of increased oxidative stress, or cofactor deficiency-induced uncoupling of nitric oxide synthase.

In addition to these factors that can raise the mean arterial pressure, two other factors may be important:

- Patients with end-stage renal disease are more likely to have an increase in pulse pressure and isolated systolic hypertension (London et al., 1992). Why this occurs is incompletely understood but increased aortic stiffness appears to play an important role.
- Patients with CKD may not demonstrate the normal nocturnal decline in blood pressure (called "nondippers"), a possible risk factor for hypertensive complications.

The optimal blood pressure in hypertensive patients with CKD is uncertain. The rate of loss of GFR appears to be more rapid when the mean arterial pressure remains at or above 100 mmHg (which reflects a diastolic pressure of 80 to 85 mmHg in the absence of systolic hypertension). To slow progression of CKD, the optimal blood pressure depends in part on the degree of proteinuria.

We recommend a blood pressure goal of less than 130/80 mmHg, which is consistent with JNC 7 and the K/DOQI Clinical Practice Guidelines on hypertension and antihypertensive agents in CKD. However, evidence from the Modification of Diet in Renal Disease study, the AASK trial, and a meta-analysis from the ACE inhibition and Progressive Renal Disease (AIPRD) study group suggest that an even lower systolic pressure may be more effective in slowing progressive renal disease in patients with a spot urine total protein-to-creatinine ratio =1000 mg/g (which represents protein excretion of greater than 1000 mg/day). Caution is advised about lowering the systolic blood pressure below 110 mmHg.

The desired degree of blood pressure control typically requires combination therapy in patients with CKD. The regimen should include an ACE inhibitor or angiotensin II receptor blocker, which are the preferred drugs to prevent progressive proteinuric CKD, and a diuretic for fluid control

A loop diuretic is recommended for the treatment of hypertension and edema in patients with CKD. The thiazide diuretics in conventional dosage become less effective as monotherapy when the GFR falls below 20 ml/min. They do, however, produce an additive effect when administered with a loop diuretic for refractory edema.

Calcium channel blockers are also effective in the hypertension of CKD. These agents are relatively unique in that they seem to be more effective in patients who are volume expanded.

8.2 Volume overload

Sodium and intravascular volume balance are usually maintained via homeostatic mechanisms until the GFR falls below 10 to 15 ml/min. However, the patient with mild to moderate CKD, despite being in relative volume balance, is less able to respond to rapid infusions of sodium and is therefore prone to fluid overload. As kidney function declines, most patients develop sodium retention and extracellular volume expansion. They may complain of ankle swelling or shortness of breath as a result of pulmonary edema.

Patients with CKD and volume overload generally respond to the combination of dietary sodium restriction and diuretic therapy, usually with a loop diuretic given daily.

8.3 Anemia

Anemia has been defined by the World Health Organization (WHO) as a hemoglobin (Hgb) concentration below 13.0 g/dl for adult males and post-menopausal women, and a Hgb below 12.0 g/dl for pre-menopausal women . Based upon these criteria, nearly 90 percent of patients with a GFR less than 25 to 30 ml/min have anemia, many with Hgb levels below 10 g/dl.

Anemia is an almost universal complication of CKD. It contributes considerably to reduced quality of life of patients with CKD and has been increasingly recognized as an adverse risk factor. Renal anemia is typically an isolated normochromic, normocytic anemia with no leukopenia or thrombocytopenia.

It is principally due to reduced renal erythropoietin production and, to a lesser degree, to shortened red cell survival and decreased responsiveness to the hormone.

Anemia can develop well before the onset of uremic symptoms due to ESRD and is a common feature in many patients with CKD who do not require dialysis, with decreasing hemoglobin levels as GFRs decline below 60 ml/min per 1.73 m². As an example, based upon over 15,000 participants in the NHANES survey, the prevalence of anemia (Hbg <12 g/dL in men and <11 g/dL in women) increased from one percent at an estimated GFR of 60 ml/min per 1.73 m² to 9 percent at an estimated GFR of 30 ml/min per 1.73 m² and to 33 to 67 percent at an estimated GFR of 15 ml/min per 1.73 m². Kazmi et al. (2001) in a study on anemia in pre-dialysis patients have demonstrated that even among CKD patients in the serum creatinine <2mg/dl category, 24% of the patients had hemoglobin levels <11g/dl (Figure 1). Anemia has also been implicated as a contributing factor in many of the symptoms associated with reduced kidney function. These include fatigue, depression, reduced exercise tolerance, dyspnea, and cardiovascular consequences, such as left ventricular hypertrophy (LVH) and left ventricular systolic dysfunction. It is also associated

with an increased risk of morbidity and mortality principally due to cardiac disease and stroke, and with an increased risk of hospitalization, hospital length of stay, and mortality in patients with predialysis CKD.
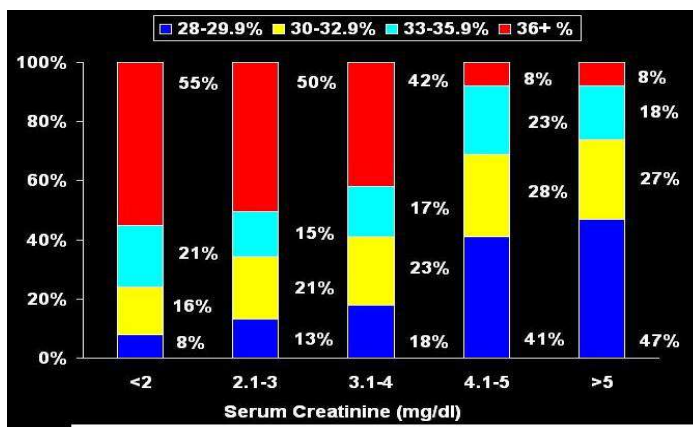

Fig. 1. Prevalence of anemia in patients with different stages of CKD (Kazmi et al., Am J Kidney Dis, 2001).

8.4 Hyperkalemia

The ability to maintain potassium excretion at near normal levels is generally maintained in patients with renal disease as long as both aldosterone secretion and distal flow are maintained (Gonik et al., 1971; Hsu & Chertow, 2002). Thus, hyperkalemia generally develops in the patient who is oliguric, or who has an additional problem such as a high potassium diet, increased tissue breakdown, or hypoaldosteronism (due in some cases to the administration of an ACE inhibitor or ARB) (Gennari & Segal, 1995). Impaired cell uptake of potassium also may contribute to the development of hyperkalemia in advanced CKD. Unlike patients with acute kidney failure, those with CKD may tolerate high plasma potassium concentrations without electrocardiographic changes or arrhythmias.

Hyperkalemia due to ACE inhibitor or ARB therapy is most likely to occur in patients in whom the serum potassium concentration is elevated or in the high normal range prior to therapy. In this setting, institution of a low-potassium diet or concurrent use of a loop diuretic (to increase urinary potassium losses) often ameliorates the degree of hyperkalemia. In selected patients, low dose Kayexalate (5 grams with each meal) can be used to lower the serum potassium concentration without the side effects associated with larger doses. In addition to treating hyperkalemia, there are several measures that can help prevent hyperkalemia in patients with CKD. These include ingestion of a low potassium diet (eg, less than 40 to 70 meq/day [1500 to 2700 mg/day]) and avoiding, if possible, the use of drugs that raise the serum potassium concentration such as nonsteroidal antiinflammatory drugs (Allon, 1995). Nonselective beta-blockers make the postprandial rise in the serum potassium concentration but do not produce persistent hyperkalemia.

Spontaneous hypokalemia is uncommon in CKD, but it can be seen in salt wasting nephropathy, Fanconi's syndrome, hereditary or acquired tubulointerstitial disease, and renal tubular acidosis .in patients with CKD, hypokalemia is usually caused by low dietary potassium intake combined with high doses of diuretics or by gastrointestinal loss.

8.5 Metabolic acidosis

There is an increasing tendency to retain hydrogen ions among patients with CKD. (Uribarri et al., 1995; Warnock, 1988; Widmer et al., 1979). This can lead to a progressive metabolic acidosis with the serum bicarbonate concentration tending to stabilize between 12 and 20 meq/l, and rarely falling below 10 meq/l (Warnock, 1988; Walia et al., 1986).

Previously, exogenous alkali was not usually given to treat the generally mild metabolic acidosis (arterial pH generally above 7.25) in asymptomatic adults with CKD. This was primarily due to concerns related to the exacerbation of volume expansion and hypertension. However, these concerns appear to be overstated. The treatment of acidosis is desirable to prevent osteopenia and muscle catabolism. In fact, bone buffering of some of the excess hydrogen ions is associated with the release of calcium and phosphate from bone, which can worsen the bone disease. Uremic acidosis can increase skeletal muscle breakdown and diminish albumin synthesis, leading to loss of lean body mass and muscle weakness. The administration of bicarbonate increases serum albumin and the lean body mass (de Brito-Ashurst et al., 2009).

It is now recommended to start alkali therapy to maintain the serum bicarbonate concentration above 23 meq /l (de Brito-Ashurst et al., 2009). If alkali is given, sodium bicarbonate (in a daily dose of 0.5 to 1 meq/kg per day) is the agent of choice. Sodium citrate (citrate is rapidly metabolized to bicarbonate) may be used in patients who are unable to tolerate sodium bicarbonate, since it does not produce the bloating associated with bicarbonate therapy. Sodium citrate should be avoided in the rare patient who may be taking aluminum-containing antacids since it markedly enhances intestinal aluminum absorption.

An alternative method to correct the metabolic acidosis in patients on maintenance dialysis is to increase the bicarbonate concentration in the dialysate. Levels as high as 42 meq/l may be required with hemodialysis to prevent predialysis acidosis. This regimen is generally well tolerated and does not induce significant postdialysis alkalosis.

8.6 Renal osteodystrophy

Four main types of renal bone disease can be seen in patients with CKD. These are osteitis fibrosa cystica, adynamic bone disease, osteomalacia, and mixed renal osteodystrophy, with the last disorder being a mixture of the first three. The prevalence of the different types of bone disease has changed over the last several decades. At present, the most common disorder is adynamic bone disease, with osteitis fibrosa, osteomalacia, and mixed disease less frequently observed.

A tendency toward phosphate retention begins early in renal disease, due to the reduction in the filtered phosphate load. Although this problem is initially mild with hyperphosphatemia being a relatively late event, phosphate retention is intimately related to the common development of secondary hyperparathyroidism that play an important role in the pathogenesis of bone disease and in other uremic complications.

Dietary phosphate restriction may limit the development of secondary hyperparathyroidism in patients with CKD. An intake of about 800 mg/day may be desirable and is recommended by the K/DOQI guidelines in patients with elevated phosphate and/or PTH levels.

Once the GFR falls below 25 to 30 ml/min, the addition of oral phosphate binders are usually required to prevent hyperphosphatemia (Abboud & Henrich, 2010; Sarnak et al., 2005). The K/DOQI guidelines recommend that serum phosphorus levels should be between 2.7 and 4.6 mg/dl (0.87 and 1.49 mmol/l) among patients with stage 3 and 4 CKD, and between 3.5 and

5.5 mg/dl (1.13 and 1.78 mmol/l) among those with ESRD (or stage 5 disease) (Sarnak et al., 2005). Patients are also prescribed biologically active vitamin D e.g calcitriol or vitamin D prohormones that are converted to active dihydroxylated compounds in the liver.

8.7 Malnutrition

Malnutrition is common in patients with advanced chronic renal disease because of a lower food intake (principally due to anorexia), decreased intestinal absorption and digestion, and metabolic acidosis (Kopple et al., 2000; Garg et al., 2001; Bammens et al., 2003). Among participants =60 years of age in the United States NHANES III, a GFR <30 ml/min was independently associated with malnutrition (odds ratio of 3.6) (Garg et al., 2001).

It is, therefore, desirable to monitor the nutritional status of patients with CKD. Biochemical indicators include a fall in serum albumin, transferrin, and cholesterol. Weight should be carefully monitored in patients who progress to CKD stages 4 to 5 ,these should be measured approximately every one to three months for those with estimated GFRs <20 ml/min, and more frequently if necessary for those with GFRs =15 ml/min.

8.8 The uremic syndrome

The uremic syndrome can be defined as deterioration of multiple biochemical and physiological function in parallel with progressive renal failure, thereby resulting in complex but variable symtomatology. A myriad of uremic retention solutes accumulates in the uremic patients with ESRD which are directly or indirectly attributable to deficient renal clearance that impair cell regulatory mechanisms involving the cardiovascular, gastrointestinal, hematopoietic, immune, nervous and endocrine systems.

These retained solutes are called uremic toxins when they contribute to the uremic syndrome. The uremic syndrome is characterized not only by solute accumulation but also by hormonal alterations such as decreased production of erythropoietin and calcitriol, decreased clearance of insulin, end-organ resistance to insulin and PTH. The signs and symptoms vary from one patient to another, depending partly on the rate and severity of the loss of kidney function.

Uremic toxins can be subdivided into three major groups based upon their chemical and physical characteristics:

- Small, water-soluble, non-protein-bound compounds, such as urea
- Small, lipid-soluble and/or protein-bound compounds, such as the phenols
- Larger so-called middle-molecules, such as beta2-microglobulin

8.9 Dyslipidemia

Abnormal lipid metabolism is common in patients with renal disease. Patients with CKD stage 3 develop a disturbance of lipoprotein metabolism characterized by accumulation of partially metabolized very-low-density lipoprotein particle and a disturbance in the maturation of high-density-lipoprotein .The primary finding in CKD is hypertriglyceridemia with the total cholesterol concentration usually being normal (perhaps due in part to malnutrition in some patients). Patients with CKD should be assessed for dyslipidemia, including a total cholesterol, LDL, HDL, and triglycerides.

Among patients with CKD, the degree of hypertriglyceridemia that occurs may not be sufficient to significantly increase coronary risk, but other changes have been found that might contribute to the accelerated atherosclerosis commonly seen in ESRD. First, dietary modification may be helpful for the hypertriglyceridemia. Drug therapy in patients without

renal failure may be beneficial in selected patients with isolated marked hypertriglyceridemia (serum triglycerides =500 mg/dl [=5.65 mmol/l]) who have proven coronary disease, a strong family history of Coronary heart disease (CHD), or multiple coexisting cardiac risk factors. Whether this approach is beneficial in patients with renal failure is not known, but it should be considered. Fibrate dose should be reduced in any patient with CKD stage 3 to 4, and these agents are best avoided in those with stage 5 disease.

In the patient with hypercholesterolemia, a statin can effectively and safely lower the plasma cholesterol concentration to or near acceptable levels, although low starting doses are recommended because of drug accumulation. The goal LDL-cholesterol is similar to that in patients with CHD, which has been less than 100 mg/dl (2.6 mmol/l).

Limited data suggest that lipid lowering may have an additional benefit in patients with CKD, which is slowing the rate of progression of the underlying renal disease.

8.10 Sexual dysfunction in females

Disturbances in menstruation, fertility, and sexual dysfunction are commonly encountered in women with CKD, usually leading to amenorrhea by the time the patient reaches ESRD. The menstrual cycle typically remains irregular with scanty flow after the initiation of maintenance dialysis, although normal menses are restored in some women (Holley et al., 1997; Peng et al., 2005). In others, menorrhagia develops, sometimes leading to significant blood loss and increased transfusion requirements.

The major menstrual cycle abnormality in uremic women is anovulation, resulting in infertility. Women receiving chronic dialysis also tend to experience decreased libido and reduced ability to reach orgasm (Hou, 1999; Finkelstein et al., 2007).

Although rare, pregnancy can occur in women with advanced kidney failure, but fetal wastage is markedly increased (Hou, 1999). Some residual renal function is usually present in the infrequent pregnancy that can be carried to term. Although luteinizing hormone levels are high, there is absence of the preovulatory peak in LH and estradiol concentrations. The failure of LH to rise in part reflects a disturbance in the positive estradiol feedback pathway, since the administration of exogenous estrogen to mimic the preovulatory surge in estradiol fails to stimulate LH release. In contrast, feedback inhibition of gonadotropin release by low doses of estradiol remains intact. This can be illustrated by the ability of the antiestrogen clomiphene to enhance luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion.

Women with CKD commonly have elevated circulating prolactin concentrations and galactorrhea due to increased secretion and decreased metabolic clearance. The hypersecretion of prolactin in this setting appears to be relatively autonomous, as it is resistant to maneuvers designed to stimulate or inhibit its release. Similar observations have been made in uremic males.

The elevated prolactin levels may impair hypothalamic-pituitary function and contribute to sexual dysfunction and galactorrhea in these patients. Bromocriptine treatment corrects the hyperprolactinemia in these patients but does not restore normal menses, thereby suggesting that other mechanisms are involved.

8.11 Sexual dysfunction in males

Disturbances in sexual function are a common feature of chronic kidney disease (Palmer, 2003; Holdsworth et al., 1978). Over 50 percent of uremic men complain of symptoms that include erectile dysfunction, decreased libido, and marked decline in the frequency of

intercourse (Diemont et al., 2000). Prolactin levels are elevated in CKD stage 5 and may contribute to gynecomastia and sexual dysfunction. Testosterone levels are often low-normal, and gonadotropins may be raised, implying testicular failure. This is accompanied by poor spermatogenesis, leading to low sperm counts and reduced fertility. These problems may improve, but rarely normalize with the institution of maintenance dialysis, commonly resulting in a decreased quality of life (Rosas et al., 2003). By comparison, a well-functioning renal transplant is much more likely to restore sexual activity; however, some features of reproductive function may remain impaired, particularly reduced libido and erectile dysfunction.

It is presumed that the uremic milieu plays an important role in the genesis of this problem. Other organic (and not necessarily uremic) factors that may contribute to erectile dysfunction include peripheral neuropathy, autonomic dysfunction, peripheral vascular disease, and pharmacologic therapy.

8.12 Thyroid dysfunction

The kidney normally plays an important role in the metabolism, degradation, and excretion of several thyroid hormones. It is not surprising, therefore, that impairment in kidney function leads to disturbed thyroid physiology. All levels of the hypothalamic-pituitary-thyroid axis may be involved, including alterations in hormone production, distribution, and excretion.

As a result, abnormalities in thyroid function tests are frequently encountered in uremia. However, the overlap in symptomatology between the uremic syndrome and hypothyroidism requires a cautious interpretation of these tests. Nevertheless, it is ordinarily possible in the individual uremic patient to assess thyroid status accurately by physical diagnosis and thyroid function testing.

Epidemiologic data suggests that predialysis patients with CKD have an increased risk of hypothyroidism (Lo et al., 2005; Chonchol et al., 2008). Many cases are subclinical. Free thyroxin [T4] and serum thyroid stimulating hormone [TSH] are usually normal but most patients with ESRD have decreased plasma levels of free triiodothyronine (T3), which reflect diminished conversion of T4 (thyroxine) to T3 in the periphery (Kaptein et al., 1988). This abnormality is not associated with increased conversion of T4 to the metabolically inactive reverse T3 (rT3), since plasma rT3 levels are typically normal. This finding differentiates the uremic patient from patients with chronic illness. In the latter setting, the conversion of T4 to T3 is similarly reduced, but the generation of rT3 from T4 is enhanced.

8.13 Insulin metabolism

Impaired tissue sensitivity to insulin occurs in almost all uremic subjects and is largely responsible for the abnormal glucose metabolism seen in this setting (Mak & DeFronzo, 1992).

Both experimental and clinical studies suggest that hepatic glucose production and uptake are normal in uremia and that skeletal muscle is the primary site of insulin resistance (Androgue, 1992). How this occurs is not clear, but a post-receptor defect is of primary importance (Smith & DeFronzo, 1982). Furthermore, the abnormality appears to specifically involve glycogen synthesis, as the rate of glucose oxidation is relatively normal. It is of interest in this regard that other actions of insulin such as promoting potassium uptake by the cells, and inhibiting proteolysis are also maintained in renal failure.

Accumulation of a uremic toxin or toxins and excess parathyroid hormone (PTH), resulting from abnormalities in phosphate and vitamin D metabolism are thought to be responsible

for the insulin resistance (McCaleb et al., 1985). As an example, the observation that tissue sensitivity to insulin can be substantially improved by dialysis is consistent with a role for uremic toxins. The expected response to impaired tissue sensitivity would be an augmentation in insulin secretion in an attempt to normalize glucose metabolism. In many cases, however, insulin secretion tends to be blunted; these patients tend to have the greatest impairment in glucose tolerance.

One factor that can suppress insulin release in CKD is the associated metabolic acidosis. In addition, deficiency of calcitriol (1,25-dihydroxyvitamin D) and excess PTH may interfere with the ability of the beta cells to augment insulin secretion in response to hyperglycemia or amino acids. A PTH-induced elevation in the intracellular calcium concentration may be responsible for the impairment in insulin release by decreasing both the cellular content of ATP and Na-K-ATPase pump activity in the pancreatic beta cells.

There is little change in the metabolic clearance rate of insulin in renal disease until the GFR has fallen to less than 15 to 20 ml/min. At this point, there is a dramatic reduction in insulin clearance which is also mediated by a concomitant decline in hepatic insulin metabolism. The hepatic defect may be induced by a uremic toxin, since it is largely reversed with adequate dialysis.

Insulin requirements show a biphasic course in diabetic patients with renal disease. It is not uncommon for glucose control to deteriorate as renal function deteriorates, as increasing insulin resistance can affect both insulin-dependent and non-insulin-dependent diabetics. Thus, insulin requirements may increase in the former, while the institution of insulin therapy may be necessary in the latter.

In comparison, the marked fall in insulin clearance in advanced renal failure often leads to an improvement in glucose tolerance. This may allow a lower dose of insulin to be given or even the cessation of insulin therapy. Decreased caloric intake, due to uremia-induced anorexia, also may contribute to the decrease in insulin requirements.

8.14 Hypoglycemia

An unusual manifestation of disturbed glucose metabolism in CKD is the development of spontaneous hypoglycemia. This complication can be seen in both diabetic and nondiabetic subjects. As an example, in a retrospective analysis of 243,222 patients, the incidence of hypoglycemia was significantly higher among patients with CKD (defined as estimated GFR <60 ml/min per 1.73 m²) compared with patients without chronic kidney disease, both among those with diabetes (10.72 versus 5.33 per 100 patient-months, respectively) and without diabetes (3.46 versus 2.23 per 100 patient-months, respectively) (Moen et al., 2009).

Multiple factors may play a contributory role. These include decreased caloric intake, reduced renal gluconeogenesis due to the reduction in functioning renal mass, impaired release of the counter-regulatory hormone epinephrine due to the autonomic neuropathy of renal failure, concurrent hepatic disease, and decreased metabolism of drugs that might promote a reduction in the plasma glucose concentration such as alcohol, propranolol and other nonselective -blockers, and disopyramide.

8.15 Psychological manifestations

Psychiatric illness is common among patients with chronic disorders, particularly in those with ESRD. In a review based upon United States Renal Disease Systems (USRDS) data (Kimmel et al., 1998) the psychological problems associated with CKD included affective

disorders, particularly depression, organic brain diseases eg, dementia and delirium drug-related disorders (such as alcoholism), schizophrenia and other psychoses and personality disorders.

These disorders account for a 1.5 to 3.0 times higher rate of hospitalization among dialysis patients compared to those with other chronic illnesses, thereby resulting in significant morbidity. In the previous study of approximately 175,000 dialysis patients, 9 percent were hospitalized with a mental disorder during a one-year period. A subsequent study from Japan reported a one-year 10.6 percent incidence of psychiatric disorders in dialysis patients (Fukunishi et al., 2002). Dementia, delirium, and major depression were the most common disorders in this four-year follow-up study.

Patients maintained on hemodialysis are more likely to be hospitalized for a psychiatric disorder than are those treated with peritoneal dialysis. This difference may be due to patient selection for a particular dialysis modality or the increased incidence among hemodialysis patients of disruptive behaviors that may lead to hospitalization. Overall, the type of dialysis modality does not appear to have a significant impact upon symptoms related to depression, sexual function, and life satisfaction.

8.16 Gastrointestinal manifestations

Gastrointestinal complications are common in advanced CKD and in some cases may be the first or only complaint on presentation. Anorexia, nausea, vomiting, and uremic fetor are common manifestations of uremia. Vomiting may occur without nausea and is often prominent in the early morning. Stomatitis, gastritis and enteritis can develop with ESRD in patients not treated with dialysis or transplantation. In one study of 60 patients with ESRD, panendoscopy revealed esophagitis, gastritis, and duodenitis in 13, 22, and 60 percent of patients, respectively, while biopsies showed histologic evidence of gastritis and duodenitis in 46 and 43 percent, respectively (Margolis et al., 1978). The incidence of gastritis appears to decline with increasing duration of dialysis. The pathogenesis of mucosal inflammation in these patients is unclear.

In general, there is an increased risk of bleeding in hemodialysis patients because of uremia-induced platelet dysfunction as well as the intermittent use of heparin with dialysis treatments. These systemic abnormalities may in part help explain the perceived higher incidence of upper gastrointestinal (UGI) bleeding in patients with ESRD. The causes of UGI bleeding among patients with ESRD may be somewhat different and a larger study found that angiodysplasia was a more frequent cause of upper GI bleeding in patients with renal failure compared to those without renal dysfunction. In this report, 727 patients with upper GI bleeding underwent diagnostic endoscopy. Among the 60 patients with CKD, the most common causes of bleeding were gastric ulcer (37 percent), duodenal ulcer (23 percent), and angiodysplasia (13 percent). Compared to patients without renal disease, angiodysplasia as a cause of UGI bleeding was significantly more common in those with renal failure (13 versus 1.3 percent, P<0.01).

Rarely, pancreatitis is a significant clinical problem and additional reported risk factors in this patient population may include vascular disease, polycystic kidney disease, drug ingestion (possibly including valproic acid and iodixanol), and hyperparathyroidism.

Lower gastrointestinal disorders of importance in CKD patients include uremic colitis (principally of historic interest), ischemic bowel disease, spontaneous colonic perforation, fecal impaction, diverticular disease, and angiodysplasia. A positive fecal occult blood test appears to be more informative as kidney function declines. One study of 531 patients with a positive

test, for example, found that clinical significant findings increased from 24 to 33 to 43 percent in patients with normal/stage 1 CKD, stage 2/3 CKD, and stage 4/5 CKD, respectively (Bini et al., 2006). Similar findings were observed with adenomas, carcinomas, and vascular ectasias.

9. Prevention of progression of chronic kidney disease

A kidney disease that progresses to ESRD usually does so by two mechanisms; those of primary kidney disease and those of natural progression. For most CKD patients, the first evidence of natural progression is proteinuria increasing from low to heavy levels. Only later does decreasing GFR appear. However, for certain diseases such as polycystic kidney disease, a decrease in GFR or the presence of hypertension may be the heralding features.

9.1 Monitoring proteinuria

Proteinuria magnitude generally is the strongest single predictor of GFR decline. Therapy-induced proteinuria reduction slows GFR decline.The most detailed analysis of proteinuria and progression are from the Modification in Diet in Renal Disease and Ramipril Efficacy in nephropathy trials which show that for each 1.0gm reduction in proteinuria by 4 to 6 months of the antiproteinuric intervention, GFR decline is slowed by about 1 to 2 ml/min/yr. With regard to frequency of proteinuria testing, every 2 to 3 months for those with nephrotic range proteinuria and every 4 to 6 months for those with non-nephrotic proteinuria are usually sufficient to assess proteinuria trends.

9.2 Monitoring GFR trends

The GFR is equal to the sum of the filtration rates in all of the functioning nephrons; thus, estimation of the GFR gives an approximate measure of the number of functioning nephrons. A reduction in GFR implies either progression of the underlying disease or the development of a superimposed and often reversible problem, such as decreased renal perfusion due to volume depletion. An increase in GFR, on the other hand, is indicative of improvement in renal function, whereas a stable GFR in patients with renal disease implies stable disease.

The most common methods utilized to estimate the GFR in adults are the serum creatinine concentration, the creatinine clearance, and estimation equations based upon the serum creatinine concentration: the Cockcroft-Gault equation and Modification of Diet in Renal Disease (MDRD) study equation.

The K/DOQI working groups have published guidelines recommending that patients with CKD should be classified by disease stage, with each stage being defined in part by GFR estimation. In adults, the GFR should be estimated from the MDRD Study and Cockcroft-Gault equations, which take into account the serum creatinine concentration and some or all of the following variables: age, gender, race, and body size. Since the MDRD Study equation was derived from patients (largely white) with nondiabetic renal disease (mean GFR of 40 ml/min per 1.73 m^2) in the United States, it can be reliably used in such patients with significant kidney disease. It also appears to be accurate in African-Americans and those with diabetic kidney disease.

However, the estimation equations have not been validated, and may be less accurate, in some populations. These include individuals with high, normal, or near-normal renal function, children, certain ethnic groups, pregnant woman, and those with unusual muscle mass, body habitus, and weight (eg, morbid obesity or malnourished). Some therefore recommend measuring the creatinine clearance to estimate the GFR in these patients with stable renal function.

Serum creatinine and GFR estimation equations can only be used in patients with stable kidney function. With acute renal failure, for example, the GFR is initially markedly reduced but there has not yet been time for creatinine to accumulate and for the SCr to reflect the degree of renal dysfunction.

What is important to know in the patient with kidney disease is whether the GFR (and therefore disease severity) is changing or is stable. This can usually be determined by monitoring changes in the serum creatinine or the estimated GFR in patients with a relatively constant body mass and diet.

9.3 Angiotensin-converting enzyme inhibitors

The degree of proteinuria in glomerular disease tends to vary directly with the intraglomerular pressure. It was, therefore, proposed that a treatment-induced reduction in protein excretion (in the absence of a large fall in GFR) reflected a desirable decline in intraglomerular pressure, and would result in improved renal outcomes. Although both angiogenesis-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs] are kidney protective; an ACE inhibitor is the first choice because it is not clear whether ARBs are cardioprotective to the level of ACE inhibitors. ACE inhibitor should be used even if the patient is not hypertensive and regardless of the level of proteinuria. ACE inhibitors slow progression even in those with a low grade of proteinuria. Although the greatest benefit is in those with heavy proteinuria. Measures that may increase ACE inhibitor kidney protection include a low salt, reduced-protein diet, diuretic therapy, the low BP goal and statin therapy. ACE inhibitors are antiproteinuric, even in inflammatory glomerulonephritis. ACE inhibitor should be continued even if GFR decline to stage 4 CKD [15 to 29 ml/min 1.73 m^2]. To prevent hyperkalemia, dietary potassium restriction, and the concomitant use of a loop diuretic and sodium bicarbonate may be needed. Advancing the ACE inhibitor dose to tolerance may increase its antiproteinuric effect and decrease the likeihood of aldosterone escape (increasing plasma aldosterone levels during stable ACE inhibitor therapy), which may diminish the ACE inhibitor reno-protection. In addition to lowering the intraglomerular pressure, experimental studies suggest that the beneficial effect of ACE inhibitors may also be related to a number of other factors:

* Angiotensin II is a growth factor; therefore, diminishing its production may minimize glomerular hypertrophy which, by decreasing the capillary radius, can reduce the tension on the glomerular capillary wall (Fogo, 2000).
* Angiotensin II, either directly or via increased glomerular pressure, can enhance the release of extracellular matrix and collagen from mesangial and tubular cells, thereby promoting both glomerular and tubulointerstitial fibrosis (Boffa et al., 2003). This effect is mediated at least in part by enhanced release of transforming growth factor-beta, matrix proteins, platelet-derived growth factors, and plasminogen activator inhibitor-I. Administration of an ACE inhibitor and/or angiotensin II receptor blocker decreases cytokine release, due most likely to a fall in glomerular pressure and/or reversal of the direct action of angiotensin II.

The ability of ACE inhibitors and/or angiotensin II receptor blockers to block the profibrotic effect of angiotensin II may be particularly due to their effect to decrease transforming growth factor-beta and plasminogen activator inhibitor-I levels (among others), and/or increase hepatocyte growth factor concentrations. Due to these effects, ACE inhibitors and angiotensin II receptor blockers may help reverse renal sclerosis, as observed in multiple animal models of progressive kidney dysfunction (Remuzzi et al., 2002).

- An ACE inhibitor may directly improve the size selective properties of the glomerulus, thereby preventing the accumulation of macromolecules in the mesangium and a secondary increase in mesangial matrix production (Remuzzi et al., 1990). Whether this effect is related to or is independent of the associated reduction in intraglomerular pressure is not clear.
- Inhibition of angiotensin II production via ACE inhibition also lowers the release of aldosterone.
- Due to decreased degradation, ACE inhibitors increase bradykinin concentrations, which may ameliorate renal tubulointerstitial fibrosis. Support for this was provided by an animal model in which unilateral ureteral obstruction-induced interstitial fibrosis was significantly increased in bradykinin B2 receptor knockout mice (Schanstra et al., 2002). Bradykinin may dampen fibrosis by increasing extracellular matrix degradation via enhanced metalloproteinase-2 and other enzymatic activity. A similar benefit by this mechanism would not be expected with an angiotensin II receptor blocker, which does not increase bradykinin levels.

9.4 Angiotensin II receptor blockers

The renoprotective effectiveness of angiotensin II receptor blockers (ARBs) has been best described in type 2 diabetic nephropathy. It seems likely that they will have a similar renoprotective effect as ACE inhibitors in nondiabetic CKD, but supportive data are limited (Lee et al., 2006). Studies in humans have found that ARBs are as effective as ACE inhibitors in reducing protein excretion in patients with CKD (Hilgers & Mann, 2002). In a 2008 meta-analysis of randomized trials (mostly small), the reduction in proteinuria at 5 to 12 months was similar with ARBs and ACE inhibitors (ratio of means 1.08, 95% CI 0.96-1.22). In addition, the reduction in proteinuria with ARBs was significantly greater than that with amlodipine (ratio of means 0.62, 95% CI 0.55-0.70). As with ACE inhibition, there appears to be a dose effect, with greater reduction of proteinuria at higher (even supramaximal) doses in both nondiabetic and diabetic patients. In the SMART trial, for example, 269 patients with proteinuria greater than 1 g/day, despite seven weeks of the maximum approved dose of candesartan (16 mg/day) were randomly assigned to candesartan at a dose of 16, 64, or 128 mg/day. Patients who received 128 mg/day had a significantly greater reduction in proteinuria at 30 weeks compared to those who received 16 mg/day (mean difference in percent change of proteinuria of 33 percent). The blood pressure was not different between groups. Although hyperkalemia required the withdrawal of 11 patients from the trial, there was no difference in the incidence of hyperkalemia between groups. Further studies of the efficacy, safety, and cost are required before such high dose therapy can be recommended.

9.4.1 ACE inhibitors plus ARBs

The reduction in proteinuria appears to be greater when ACE inhibitors are used in combination with ARBs than with either drug alone. However, it has not been proven that combination therapy improves renal outcomes, and adverse effects are more common.

9.4.2 ARB plus aliskiren

The first effective oral direct renin inhibitor, aliskiren, was approved by the United States Food and Drug Administration in March 2007. Aliskiren lowers blood pressure to a degree comparable to most other agents. In the AVOID trial, aliskiren plus losartan was associated

with a significant 20 percent greater reduction in proteinuria compared to losartan alone, in the absence of a significantly greater effect on blood pressure (Parving et al., 2008). The role of aliskiren in preventing progression of CKD is not yet known (Ingelfinger, 2008).

9.5 Control protein intake

In a variety of animal models (such as subtotal nephrectomy and diabetic nephropathy), lowering protein intake protects against the development of glomerular scarring (called glomerulosclerosis). This effect is mediated, in part, by changes in glomerular arteriolar resistance, leading to a reduction in intraglomerular pressure and decreased glomerular hypertrophy.

Studies in humans indicate that an increase in the GFR can be induced by animal protein and by amino acid mixtures; in comparison, vegetable protein and egg whites alone produce little or no effect. Why the latter sources of protein have little hemodynamic activity is not clear, but lower concentrations of the amino acids that cause renal vasodilatation (such as glycine and alanine) and lesser stimulation of vasodilator prostaglandins may be involved. Enhanced secretion of glucagons, a direct renal vasodilator, may be a mediator of protein-induced hyper filtration (King & Levey, 1993). A high protein diet also increases the release of at least two other hormones that can raise the GFR, including insulin-like growth factor I (IGF-I) and kinins. IGF-1 is a direct renal vasodilator that can increase both renal blood flow and the GFR. In addition to a possible role in protein-induced hyperfiltration, IGF-1 may play an important role in the hyperfiltration and glomerular hypertrophy observed in type 1 diabetes mellitus. The renin-angiotensin system may also modulate the effect of protein on glomerular filtration. Angiotensin II leads to a preferential increase in efferent arteriolar resistance, causing an increase in intraglomerular pressure and hyperfiltration. Lowering angiotensin II production induces efferent dilatation, which decreases intraglomerular pressure and perhaps the GFR. However, there are conflicting data on the effect of a low protein diet on renal renin release. Both a reduction in renin gene expression (which could contribute to the protective effect of a low protein diet in renal disease) and an increase in gene expression have been described.

Intrarenal mechanisms, including tubuloglomerular feedback, may contribute to protein-induced hyper filtration (Woods, 1993). An increase in the filtered load of amino acids may enhance proximal sodium reabsorption via sodium-amino acid cotransporters in the proximal tubule. The ensuing decrease in sodium chloride delivery to the macula densa may then activate tubuloglomerular feedback, leading to an elevation in GFR in an appropriate attempt to restore macula densa delivery to normal.

Multiple well-designed randomized controlled human trials have evaluated both the efficacy and safety of protein restriction in patients with progressive CKD and reducing dietary protein intake from the usual level of about 1 to 1.5g/kg ideal weight per day, to about 0.6 to 0.8 g/kg per day slows GFR decline in those with proteinuria of more than 1gm. It is generally well tolerated and does not lead to malnutrition in patients with CKD provided caloric goals are met, dietary protein is of high biologic value, and metabolic acidosis is avoided. Dietary protein intake should be monitored periodically by urine urea excretion in 24 hour urine collections. In nutrient balance, urine urea nitrogen of 8.0g/day represents a protein intake of 50g/day, which is the target for a 70kg person. If the dietary goals are generally being met, 24-hour urine testing every 4 to 6 months is sufficient, otherwise, testing at 2- to 3-month intervals is recommended.

Therefore, we suggest the use a low protein diet (0.6 to 0.8 g/kg per day) in select predialysis patients who are highly motivated to follow such a diet. However, the adoption

of this diet should NOT preclude the initiation of dialysis in patients with severe CKD, if indicated.

9.6 Restrict salt intake

High salt intake e.g NaCl 200mmol/day, sodium 4.6g/day, NaCl 11.7g/day, can completely override the antiproteinuric effects of ACE inhibitors, ARBs, or NDHCCBs. Also, a high salt diet can activate the tissue renin angiogenesis aldosterone system, inducing renal and myocardial fibrosis, even though the circulating RAS is suppressed. The recommended NaCl intake in CKD is about 80 to 120mmol/day [2 to 3g Na, 4.6 to 6.9g NaCl]. Salt intake should be monitored periodically by 24-hour urine collection. Those achieving their NaCl goal have 80 to 120mmol Na in their 24-hour urine collection because dietary NaCl is excreted almost entirely in urine, unless there are abnormal non-renal NaCl losses.

9.7 Diuretic therapy

Diuretic therapy improves BP control and proteinuria in those treated with ACE inhibitors, or ARBs. Nevertheless, the ideal is to avoid a diuretic, if possible, because of its multiple metabolic dysfunctions, especially induction of diabetes mellitus and stimulation of the RAS.

9.8 Control blood lipids

There is indirect evidence of beneficial effects of statins on vessel stiffening and endothelial function in patients with CKD. Once renal injury has occurred, the yearly decline in GFR may be accelerated and perpetuated by dyslipidemia. However, this effect has been derived from post-hoc analyses, which are limited by unmeasured confounders that are closely correlated to dyslipidemia. If real, this effect is fairly modest.

Although statins have demonstrated cardiovascular benefits and result in improved cardiovascular outcomes in patients without CKD, the effect of statins on primary cardiovascular outcomes in patients with ESRD or less severe renal insufficiency is uncertain. Among dialysis patients, both the 4-D and AURORA trials found NO difference between statin therapy and placebo with respect to cardiovascular death, nonfatal myocardial infarction, and stroke despite significant lipid-lowering. However, the results from 4-D and AURORA should NOT be extrapolated to patients with CKD not on dialysis. There are meta-analyses and post-hoc analyses of randomized trials that have reported decreased all-cause and cardiovascularity mortality with statins.

If administered, patients with CKD should be treated with the lowest dose of statin that reduces the LDL-C to less than 100 mg/dl (2.6 mmol/l). However, more aggressive LDL-lowering to less than 70 mg/dl (1.8 mmol/l) is a reasonable option, if the additional therapy does not impose undue burdens from side effects or cost.

With respect to adverse effects, good side effect profiles with statins have been reported patients with CKD, dialysis patients, renal transplant recipients. However, accurate estimates of the risk of adverse events (especially myopathy) are not available in patients with ESRD or moderate to severe chronic renal insufficiency, since the existing clinical trials with statins in these patients have been quite small.

9.9 Smoking cessation

Smoking cessation should be encouraged, with smoking stoppage being associated with a reduced rate of progression of CKD. In an increasing number of studies, smoking also appears

to correlate with an enhanced risk of developing kidney disease (primarily nephrosclerosis) as well as increasing the rate of progression among those with existing CKD.

9.10 Avoidance of administration of nephrotoxic drugs

The administration of drugs or diagnostic agents that adversely affect renal function are a frequent cause of worsening renal function. Among patients with CKD, common offenders include aminoglycoside antibiotics (particularly with unadjusted doses), nonsteroidal antiinflammatory drugs, and radiographic contrast material, particularly in diabetics. The administration of such drugs should, therefore, be avoided or used with caution in patients with underlying CKD.

Certain drugs also interfere with either creatinine secretion or the assay used to measure the serum creatinine. These include cimetidine, trimethoprim, cefoxitin, and flucytosine. In these settings, there will be no change in GFR; the clinical clue that this has occurred is the absence of a concurrent elevation in the blood urea nitrogen (BUN).

9.11 Reduce obesity

Obesity is associated with multiple other conditions that are known to cause compromised renal function, including hypertension, diabetes, and the metabolic syndrome. However, data from the Framingham Offspring Study, the Hypertension Detection and Follow-Up Program, and the Multiphasic Health Testing Services Program suggest that obesity may be independently associated with the risk of developing CKD. Focal glomerulosclerosis and obesity-related glomerulopathy (glomerular enlargement and mesangial expansion) with associated proteinuria have been described in patients with severe obesity. Obesity-related glomerulopathy may be reversible with weight loss.

9.12 Correction of anemia

The anemia of CKD is, in most patients, normocytic and normochromic, and is due primarily to reduced production of erythropoietin by the kidney (a presumed reflection of the reduction in functioning renal mass), and to shortened red cell survival. Anemia is a common feature in many patients with CKD who do not yet require dialysis, with anemia becoming increasingly common as GFRs decline below 60 ml/min per 1.73 m^2, particularly among diabetics. As an example, based upon over 15,000 participants in the NHANES survey, the prevalence of anemia (Hbg <12 g/dl in men and <11 g/dl in women) increased from 1 percent at an eGFR of 60 ml/min per 1.73 m^2 to 9 percent at an eGFR of 30 ml/min per 1.73 m^2 and to 33 to 67 percent at an eGFR of 15 ml/min per 1.73 m^2 (Astor et al., 2002).

As stated in the 2006 K/DOQI Guidelines, the evaluation of anemia in those with CKD should begin when the Hgb level is less than 12 g/dl in females, and Hgb levels of less than 13.5 g/dl in adult males . These levels are based on the Hgb levels below the fifth percentile for the adult general population as noted in the NHANES database.

The anemia observed with CKD is largely diagnosed by excluding non-renal causes of anemia in the patient with a suitably decreased GFR. The evaluation of patients should, therefore, include red blood cell indices, absolute reticulocyte count, serum iron, total iron binding capacity, percent transferrin saturation, serum ferritin, white blood cell count and differential, platelet count, and testing for blood in stool. The content of hemoglobin in reticulocytes can also be assessed. This work-up should be performed prior to administering epoietin alfa (EPO) or darbepoietin alfa therapy. The dialysis patient is in a state of continuous iron loss from

gastrointestinal bleeding, blood drawing, and/or, most important with hemodialysis, the dialysis treatment itself. Hemodialysis patients lose an average of 2 g of iron per year. Thus, iron deficiency will develop in virtually all dialysis patients receiving EPO or darbepoetin alfa unless supplemental iron therapy is given orally or intravenously. An important issue in the diagnosis of iron deficiency in the patient with CKD or ESRD is that the laboratory criteria are markedly different from those in patients with relatively normal renal function.

Absolute iron deficiency is likely to be present in patients with ESRD when:

- The percent transferrin saturation (plasma iron divided by total iron binding capacity x 100, TSAT) falls below 20 percent
- The serum ferritin concentration is less than 100 ng/ml among predialysis and peritoneal dialysis patients or is less than 200 ng/ml among hemodialysis patients. This difference in the serum ferritin level is based upon accumulating evidence in hemodialysis patients that the maintenance of ferritin levels above 200 ng/ml is associated with decreased erythropoietin requirements.

In addition to absolute iron deficiency, it is now recognized that dialysis patients may have functional iron deficiency. This is characterized by the presence of adequate iron stores as defined by conventional criteria, but an inability to sufficiently mobilize this iron from the liver and other storage sites to adequately support erythropoiesis with the administration of erythrocyte stimulating agents (ESA).

Functional iron deficiency, which usually responds somewhat to iron therapy, must be distinguished from inflammatory iron block, which usually does not. Inflammatory iron block occurs among patients with refractory anemia due largely to an underlying inflammatory state. Both functional deficiency and inflammatory block are associated with transferrin saturation =20 percent and elevated ferritin level (between 100 to 800 ng/ml or even higher). The response to EPO and/or parenteral iron may help distinguish between functional iron deficiency and inflammatory block.

With increasing doses of ESA, ferritin levels may decrease in patients with functional deficiency but not with inflammatory iron block.

Inflammatory block is most likely present if the weekly administration of intravenous iron (50 to 125 mg) for up to 8 to 10 doses fails to result in increased erythropoiesis; instead, this course of iron therapy typically results in a progressive increase in ferritin concentration. Among patients with inflammatory block, further intravenous iron should not be given until the inflammatory condition has resolved. This is thought to be particularly important in patients with active, ongoing infections.

By comparison, among patients with functional iron deficiency, additional intravenous iron (in association with an increase in EPO dose) can be effective in increasing Hgb levels, at least over the short-term.

Serial evaluation of iron indices is necessary for the early detection of iron deficiency on dialysis once therapy with EPO or darbepoetin alfa is initiated. Serum ferritin levels and the percent transferrin saturation should be measured at baseline and then periodically thereafter.

In patients with adequate iron stores who are on maintenance oral or intravenous iron, monitoring every three months is probably adequate, especially after the first few months when iron stores are most likely to become depleted. By comparison, monitoring every one to two months is recommended in patients just starting EPO therapy or in whom the dose has been increased, in those with marginal iron status, or in those with declining serum ferritin or TSAT levels. A reduction in serum ferritin can be expected during the first few months after the initiation of EPO as iron is mobilized from iron stores and used for red cell production.

Prior to initiation of treatment with erythropoietic stimulating agents (ESA), we recommend the administration of iron therapy among hemodialysis patients with absolute iron deficiency and anemia. This is principally because ESA therapy requires significant amounts of supplemental iron for effective erythropoiesis. Although normal body stores of iron are 800 to 1000 mg, approximately 1000 mg is required among hemodialysis patients to raise hemoglobin levels from approximately 8 g/dl to 11 to 12 g/dl with the initiation of ESA therapy. After target hemoglobin levels are achieved, approximately 500 mg of iron is required every three months to maintain target levels with ESA therapy.

Among those with percent transferrin saturation =20 percent and ferritin between 200 and 500 ng/ml, we administer iron therapy prior to the use of ESAs if an underlying infection has been excluded. We do not routinely administer intravenous iron without an ESA to patients with ferritin levels above 500 ng/ml and anemia, although each patient should be individually assessed.

The most common cause of resistance to ESA is iron deficiency, which can be present at the time of initiation of ESA treatment or can develop as the result of exhaustion of iron stores due to the increase in erythropoiesis caused by ESA treatment. As shown in numerous observational and prospective studies, the administration of iron to obtain adequate iron stores increases hemoglobin levels in patients who are not on ESA treatment, as well as those who are, and lowers ESA doses.

If iron indices indicate absolute (transferrin saturation <20 percent and serum ferritin <200 ng/mL) or functional iron deficiency (transferrin saturation <20 percent and serum ferritin >200 ng/ml in the setting of ESA therapy), a sufficient amount of iron to correct the iron deficiency should be administered to raise the transferrin saturation above at least 20 to 25 percent and serum ferritin level above 200 ng/ml, we suggest administering one of the following regimens:

- 125 mg of sodium ferric gluconate complex in sucrose can be given at each consecutive hemodialysis treatment for a total of eight doses (1000 mg in total).
      OR
- 100 mg iron sucrose can be given at each consecutive hemodialysis treatment for a total of 10 doses (1000 mg in total).

Repeat the initial loading regimen if the transferrin saturation remains below 20 percent, the hemoglobin level does not increase to the target level, or the serum ferritin level remains below 200 ng/ml.

Our goal with any loading regimen is to increase hemoglobin levels and raise the transferrin saturation above at least 20 to 25 percent and serum ferritin level above 200 ng/mL, while not increasing the transferrin saturation above 50 percent or the serum ferritin level above 500 ng/ml.

Among hemodialysis patients, use of parenteral iron rather than oral iron therapy is recommended . The different parenteral preparations of iron available in the United States are iron dextran, sodium ferric gluconate complex in sucrose, and iron sucrose. These preparations are largely equivalent in efficacy. However, sodium ferric gluconate complex in sucrose and iron sucrose are much safer than iron dextran, which is associated with a significant risk of anaphylaxis. Iron replete patients are characterized by transferrin saturation levels between 20 to 50 percent and serum ferritin levels between 200 to 500 mg/l. Among such patients receiving erythropoietin stimulating agents, weekly administration of parenteral iron is sufficient to maintain Hgb.

As previously mentioned, the anemia of CKD, if left untreated, can result in deterioration in cardiac function, and decreased cognition and mental acuity. It can also be accompanied by debilitating symptoms, such as fatigue, weakness, lethargy, anorexia, and sleep disturbances. In addition, anemic patients commonly lack the stamina needed to perform normal daily activities or to work.

Furthermore, anemia in patients with CKD is also associated with an increased risk of morbidity and mortality principally due to cardiac disease and stroke, and with an increased risk of hospitalization, hospital length of stay, and mortality in patients with predialysis CKD.

9.12.1 Administration of erythropoiesis-stimulating agents

Correction of anemia with erythropoiesis-stimulating agents is associated with some clinical benefits. These include improvements in quality of life, increased energy levels, greater capacity for work and exercise, restored sexual function, improved appetite and participation in social activities, as well as reduced depression and fatigue.

The erythropoietin deficiency evident in patients with CKD can be corrected by the exogenous administration of erythropoiesis-stimulating agents. Two such agents are currently available in the United States:

- Epoetin alfa (recombinant human erythropoietin)
- Darbepoetin alfa, a unique molecule that stimulates erythropoiesis with a longer half-life than rHuEPO

9.12.2 Epoetin alfa (recombinant human erythropoietin [rHuEPO]

Several general principles govern the administration of recombinant human EPO

- The response to EPO is dose-dependent, but varies greatly among patients.
- The response is dependent on the route of administration (intravenous versus subcutaneous) and the frequency of administration. With subcutaneous administration, frequency is not as important as with the intravenous route. Response is less dependent on route of administration for darbepoetin alfa than for epoetin.
- The response may be limited by low iron stores, bone marrow fibrosis, infection, inflammation, inadequate dialysis, and other conditions.
- Hypertension may complicate therapy, particularly if the hemoglobin is raised quickly. This is primarily limited to patients undergoing dialysis. We recommend that target hemoglobin levels in dialysis patients treated with EPO or darbepoetin alfa should be maintained between 10 and 12 g/dl. In addition, the Hgb target should NOT exceed 13 g/dl.

The vast majority of cases of recombinant human erythropoietin (EPO) - related acquired pure red cell aplasia (PRCA) have occurred in patients treated with a particular epoetin alfa product. The underlying cause may be organic compounds (leached by polysorbate from uncoated rubber stoppers in prefilled syringes) that are acting as adjuvants, resulting in anti-EPO antibody development. Virtually all reported cases of anti-EPO antibody mediated PRCA have occurred in patients with chronic kidney disease who have received the drug subcutaneously. EPO-induced PRCA should be considered in the patient with significant anemia who has been treated with EPO for at least three to four weeks, and has previously responded to treatment with EPO. The condition is characterized by a sudden decline in hemoglobin level despite continued use of EPO, markedly reduced reticulocyte count, and normal white blood cell (WBC) and platelet counts. To definitively diagnose

EPO-induced PRCA, a bone marrow aspirate and evaluation for the presence of neutralizing anti-EPO antibodies should be performed. The bone marrow reveals severe erythroid hypoplasia, with less than five percent red blood cell precursors, and there may be evidence of a block in the maturation of erythroid precursors. Platelet and white cell precursors are entirely normal. Anti-EPO antibodies are detected by radioimmunoprecipitation assay (RIPA), enzyme linked immunosorbent assays (ELISA), or other assay, as available. Cessation of all erythropoietic stimulating agents with NOT switching to an alternative EPO product or to darbepoetin alfa in patients with PRCA is recommended. Patients should be transfused for symptomatic anemia.

Given that spontaneous remissions after cessation of EPO therapy are rare, the administration of immunosuppressive therapy in most patients is recommended. Initial therapy consisting of prednisone (1.0 mg/kg per day) plus oral cyclophosphamide (50 to 100 mg per day) for a maximum of three to four months. A reasonable alternative for first-line therapy is cyclosporine alone at a dose of 200 mg daily (or 100 mg twice daily) for a maximum of three to four months. Patients who do not respond to initial treatment with either oral cyclophosphamide plus prednisone or with cyclosporine alone may be subsequently treated with the other regimen.

9.12.3 Dose of EPO

The initial dose of EPO should vary based upon the baseline hemoglobin level, overall clinical setting, mode of administration, and the target hemoglobin level. A large number of studies have found that there is wide interpatient variability, as the dose of EPO required to reach hemoglobin levels above 11 g/dl among hemodialysis patients ranges from less than 50 to more than 300 U/kg three times per week.

In general, at a starting dose of 100 U/kg given intravenously three times per week, 90 percent of patients will attain a hemoglobin level of 11 to 12 g/dl, compared to 70 percent who will reach this level with 50 U/kg given intravenously three times per week. The logic of starting with the higher dose and then titrating down is that a month of therapy may be wasted on the nonresponders if the lower dose is used initially. In addition, titrating up from a smaller initial dose allows the hematocrit to rise more smoothly and more economically than with the titrate down approach.

In addition, numerous studies have found that intravenous therapy may also require, on average, approximately 30 percent more EPO than with the subcutaneous route. Thus, if subcutaneous doses are given, an initial dose for adults is 80 to 120 U/kg per week (typically 6000 U/week) given in one to three doses.

9.12.4 Dosage adjustments

In general, to attain hemoglobin levels of 11 g/dl or higher, a dose increase of 25 percent would be appropriate after four weeks if initial dosing levels do not result in a rate of increase in the hemoglobin of approximately 0.3 to 0.5 g/dl per week. Patients with hemoglobin levels that are increasing at this rate generally do not need adjustments in the EPO dose. Once the desired hemoglobin level is reached, smaller changes in the EPO dose, either titrating up or down, are usually satisfactory to maintain desired levels. Changing the dose of EPO more than once over a two- to four-week period is unnecessary in most instances.

Some patients respond to the administration of EPO with a marked acceleration in hemoglobin values. Among those with increases in hemoglobin of greater than 2.5 to 3 g/dl

per month, the EPO dose should be reduced by at least 25 percent. Some clinicians recommend holding EPO for a short period of time (i.e., one week) before resuming treatment at the reduced dosing level if the hemoglobin exceeds the target value, while others recommend that EPO doses not be held but instead be reduced in dose. For hemodialysis patients in whom EPO administration has been initiated or the dose has recently changed, the hemoglobin should be measured once per week to adequately assess the response; by comparison, the hemoglobin of patients with stable hemoglobin levels and EPO dose can be assessed every two to four weeks, although in many dialysis facilities weekly hemoglobin levels are commonly obtained.

9.12.5 Hyporesponsivess to EPO

Some patients are relatively resistant to EPO and require large doses. This may be an important clinical observation since a poor response to EPO therapy may be associated with increased mortality. Higher doses of EPO have also been associated with an increased mortality, an effect that persists after adjustment for the usually lower hematocrit in such patients A large EPO requirement is defined as either the requirement of excessive doses during initiation of therapy, or inability to achieve or maintain target Hgb levels despite the large dose in the iron-replete patient. Different guidelines have suggested different definitions:

- 450 U/kg per week intravenous EPO or 300 U/kg per week subcutaneous EPO, per K/DOQI (NKF-DOQI, 2001).
- 300 U/kg per week of EPO (approximately 20,000 U/week) and 1.5 mcg/kg per week of darbepoetin alfa (approximately 100 mcg/week), per the revised European Guidelines (Locatelli et al., 2004).

The most common cause of resistance to EPO is absolute iron deficiency which may be due to external blood losses and/or exhaustion of iron stores due to an increase in erythropoiesis caused by EPO treatment. Additional causes include the following:

- Bone disease due to secondary hyperparathyroidism;
- Occult malignancy and unsuspected hematologic disorders
- Multiple myeloma/myelofibrosis/myelodysplastic syndrome.
- Chronic inflammation (with inhibition possibly due to enhanced cytokine production)
- Although now rare, the accumulation of aluminum in bone.
- Hemoglobinopathies, as patients with sickle cell disease or trait may have an inadequate response to the administration of EPO.
- The administration of angiotensin converting enzyme inhibitors and/or angiotensin II receptor antagonists.
- Development of pure red cell aplasia associated with the presence of neutralizing anti-erythropoietin antibodies in patients treated with particular brands of EPO by the subcutaneous route.
- Presence of HIV infection.

9.12.6 Darbepoetin alfa

Darbepoetin alfa is biochemically distinct from rHuEPO. It contains up to 22 sialic acid molecules (compared with a maximum of 14 for rHuEPO), giving it higher potency and an approximately three times longer half life than that of rHuEPO (25.3 versus 8.5 hours) following intravenous administration, and.approximately twofold longer than that of subcutaneously administered rHuEPO (Macdougall et al., 1999).

Clinical studies performed in rHuEPO-naive patients (defined as patients who had not received rHuEPO within 12 weeks) confirmed that darbepoetin alfa corrects anemia in patients with CKD who have not previously been exposed to hematopoietic stimulators. Darbepoetin alfa, compared with rHuEPO, controls hemoglobin (Hb) with an extended dosing interval. In patients with CKD who are not on dialysis, subcutaneous darbepoetin alfa administered once weekly at an initial dose of 0.45 μg/kg or once every two weeks at a median dose of 60 μg achieved target Hb concentrations in 93 to 97 percent of patients in a median time of five to seven weeks (Locatelli et al., 2001). As with rHuEPO, darbepoetin alfa has beneficial effects on quality of life via its ability to correct renal anemia. Interim data from a United States study performed in 48 evaluable rHuEPO-naive patients with CKD revealed improvements in 20 of the 22 different measures of health-related quality of life after 16 weeks of treatment with darbepoetin alfa (Bahman et al., 2002). Over the same period, there was a mean increase in Hb levels of 3.3 g/dl. Several large trials have confirmed that patients stabilized on either subcutaneous or intravenous rHuEPO can be successfully switched to darbepoetin alfa given at extended dosing intervals of once weekly or once every two weeks, with maintenance of a constant Hgb (mean change of –0.08 to 0.16 g/dl) after 28 to 36 weeks of treatment.

9.12.7 Continuous Erythropoiesis Receptor Activator (C.E.R.A)

Alternative bioengineering techniques to prolong the half life of EPO further resulted in the development of C.E.R.A., which is a pegylated derivative of epoetin beta with an elimination half-life of around 130 hours when it is administered either intravenously or subcutaneously. Phase III studies suggested that many patients are able to maintain with once-monthly administration of C.E.R.A., and a superiority [PATRONUS] suggested greater efficacy with this frequency of administration compared with once monthly dosing of darbepoetin alfa when it is administered intravenously to hemodialysis patients.

9.12.8 Epomimetics

The discovery of a drug that can mimic the action of erythropoietin is another method for eliminating the need for recombinant EPO in renal failure (Vadas et al., 2008). Evidence in support of this possibility was provided by a study in which a number of short peptides were evaluated as possible agonists of the EPO receptor. Peptides whose sequence matched a minimum consensus sequence of only 14 amino acids bound to and activated the EPO receptor. This observation provides strong experimental evidence that the EPO-EPO receptor complex requires only a small number of contact points for full effect.
Hematide is a synthetic peptide-based ESA with an amino acid sequence that is unrelated to erythropoietin. It is currently undergoing evaluation in clinical trials.

9.13 Management of hyperparathyroidism

The treatment of secondary hyperparathyroidism in CKD has evolved based upon new insights into the pathogenesis and clinical features of this disorder, the recognition that abnormal calcium and phosphate homeostasis may impact upon morbidity and mortality as well as mineral homeostasis, and the development of new therapeutic agents that can suppress parathyroid hormone (PTH) without exacerbating hyperphosphatemia and causing hypercalcemia.

Because of the interdependence of calcium, phosphate, vitamin D and PTH, it is difficult to elucidate the primary and proximate causes of parathyroid gland dysfunction in patients with CKD. In addition, no single pharmacological intervention is sufficient to completely restore disordered calcium and phosphate homeostasis. The medical management of secondary hyperparathyroidism in patients with CKD principally involves the use of the combination of phosphate binders, active vitamin D analogs, and/or calcimimetics (which increase the sensitivity of the CaSR to calcium), with differences in management based in part upon the degree of renal dysfunction and whether the patient is on dialysis.

Kidney failure disrupts systemic calcium and phosphate homeostasis and affects the bone, gut, and parathyroid glands. This occurs because of decreased renal excretion of phosphate and diminished renal hydroxylation of 25-hydroxyvitamin D to calcitriol (1,25-dihydroxyvitamin D).

Circulating calcitriol levels begin to fall when the GFR is less than 40 ml/min (occasionally even less than 80 ml/min and are typically markedly reduced in subjects with end-stage renal failure. The loss of functioning renal tissue and physiologic suppression by hyperphosphatemia participate in the decline in calcitriol synthesis. Thus, progressive kidney dysfunction results in hyperphosphatemia and calcitriol deficiency. These ultimately result in hypocalcemia. These abnormalities directly increase PTH levels via different mechanisms.

The CaSR [calcium-sensing receptor] which is highly expressed in the parathyroid glands, permits variations in the serum calcium concentration to be sensed by the parathyroid gland, leading to the desired changes in PTH secretion. The fall in serum calcium concentration with renal failure, as sensed by the CaSR, is a potent stimulus to the release of PTH.

There are reductions in calcitriol-regulated calcium absorption in the gut and calcium release from bone, both of which promote the development of hypocalcemia; this is a potent stimulus to the release of parathyroid hormone (PTH), as previously mentioned.

Calcitriol acts on the vitamin D receptor (VDR) in the parathyroid gland to suppress PTH transcription, but not PTH secretion. The absence of vitamin D also decreases calcium and phosphorus absorption in the gastrointestinal tract. The net effect of low vitamin D levels is to directly increase PTH production due to removal of the normal suppressive effect of calcitriol on the parathyroid glands, and indirectly increase secretion through the gastrointestinal mediated hypocalcemic stimulus.

A decrease in calcitriol levels also lowers the number of vitamin D receptors in the parathyroid cells. The lack of calcitriol and the decreased number of receptors may both directly promote parathyroid chief cell hyperplasia and nodule formation through potential non-genomic effects.

If the physiologic abnormalities are not corrected, renal bone disease, referred to as renal osteodystrophy, will develop. Although frequently asymptomatic, this disorder can result in weakness, fractures, bone and muscle pain, and avascular necrosis. These symptoms and signs do not generally occur until the patient is undergoing maintenance dialysis.

There are several forms of renal osteodystrophy, including osteitis fibrosa cystica, adynamic bone disease, and osteomalacia. In some patients, there is evidence of more than one type, which is called mixed osteodystrophy. Osteitis fibrosa cystica and mixed osteodystrophy are largely the direct result of increased PTH levels, while adynamic bone disease is a consequence of excessive suppression of the parathyroid gland with current therapies.

9.14 Chronic kidney disease - mineral and bone disorder (CKD-MBD)

The 2009 KDIGO practice guidelines were developed to provide recommendations for the evaluation and management of chronic kidney disease-mineral and bone disorder (CKD-MBD) (KDIGO, 2009). The term CKD-MBD was created to describe the syndrome associated with mineral, bone, and calcific cardiovascular abnormalities. The guidelines were formulated in an attempt to minimize the morbidity and mortality associated with abnormal mineral metabolism, abnormal bone process, and extraskeletal calcification.

Stepped treatment approach in patients with CKD grades 3 through 5 not yet on dialysis with PTH levels higher than target level:

Step 1. Among patients with serum phosphate levels greater than target levels, first restricting dietary phosphate intake. Although the optimal limit is unclear, we usually limit phosphate intake to 900 mg per day.

Step 2. Among patients with serum phosphate levels greater than target levels despite dietary phosphorus restriction after two to four months, the administration of phosphate binders is recommended. The two principal options are calcium and non-calcium based phosphate binders:

- For patients with an initial serum calcium levels less than 9.5 mg/dl (<2.37 mmol/l), a calcium containing phosphate binder may be administered as long as hypercalcemia does not develop.

- For patients with an initial serum calcium level greater than than 9.5 mg/dl (<2.37 mmol/l), we recommend a non-calcium based phosphate binder rather than a calcium-containing phosphate binder. Either sevelamer or lanthanum carbonate can be given in this setting.

Among predialysis patients with stage 3 to 5 CKD and elevated plasma intact PTH, treatment with ergocalciferol be initiated if nutritional vitamin D deficiency exists, as demonstrated by a 25(OH)-vitamin D (calcidiol) level of less than 30 ng/ml. After initiating treatment, serum calcium and phosphorus should be monitored quarterly, and continued need for supplementation with ergocalciferol can be re-evaluated annually. If the serum level of corrected total calcium exceeds 10.2 mg/dl (2.54 mmol/l), ergocalciferol therapy should be discontinued.

Step 3. If elevated PTH levels remain despite optimal ergocalciferol and phosphate binder therapy over a six-month period, administration of low dose active oral vitamin D analog is recommended. Any one of the available active oral agents (calcitriol, alfacalcidol, doxercalciferol, or paricalcitol) may be administered using cost and formulary availability as guides. The optimal regimen is not clear. Treatment with a vitamin D analog should not be given to predialysis patients with stage 3 to 5 CKD with elevated serum phosphate levels. A vitamin D analog should also not be given unless the corrected serum total calcium concentration is less than 9.5 mg/dL (<2.37 mmol/L). In addition, initiation of vitamin D supplementation requires close outpatient follow-up to avert severe hypercalcemia, with serum calcium and phosphate being measured at least every three months. If the serum level of corrected total calcium exceeds 10.2 mg/dl (2.54 mmol/l), ergocalciferol therapy and all forms of vitamin D therapy should be discontinued.

Step 4. Among predialysis patients with secondary hyperparathyroidism that is refractory to therapy with vitamin D analogues, calcium supplements, and phosphate binders, cinacalcet may be useful. However, the use of cinacalcet in early stages of CKD is

highly controversial. Some experts and the KDIGO working group recommend NOT giving cinacalcet given the paucity of data concerning efficacy and safety in predialysis patients with CKD (Levin et al., 2008). Alternatively, parathyroidectomy could be considered for patients with refractory hyperparathyroidism and hypercalcemia not responsive to medical therapy.

If cinacalcet is administered, however, laboratory values should be monitored closely (weekly after starting therapy or change in dose) because of the risk of hypocalcemia and elevations of serum phosphate. The initial dose of 30 mg/day should be cautiously titrated upwards every two weeks only if the serum calcium level is greater than 8.4 mg/dL (2.1 mmol/liter) and PTH is higher than the target range.

Stepped approach to the management of hyperparathyroidism and bone mineral abnormalities in dialysis patients:

Steps 1 and 2 Serum calcium, albumin, phosphate, 25(OH) vitamin D and intact PTH levels are measured initially and then on an ongoing basis. The initial focus in managing secondary hyperparathyroidism should be the prevention and management of hyperphosphatemia.

As a first step, a dietary restriction of 900 mg/day of phosphorus is appropriate. There should be an emphasis on high biologic sources of phosphorus (meats, eggs) and avoidance of lower nutritional sources (certain vegetables, colas).

Serum phosphate and calcium levels are next optimized, which involves treating hyperphosphatemia without causing hypercalcemia. This is difficult to achieve with thrice weekly hemodialysis.

We suggest the following interventions based upon serum phosphate and calcium levels.

- Phosphate <5.5 mg/dl (<1.78 mmol/l) and calcium <9.5 mg/dL (<2.37 mmol/l) — Calcium-based phosphate binders should be administered. Daily elemental calcium intake from binders to less than 1,500 mg, and total elemental calcium from diet and binders to less than 2,000 mg (in the presence of concurrent therapy with active vitamin D analogues) is recommended. Either calcium carbonate or calcium acetate can be administered.
- Phosphate <5.5 mg/dl (<1.78 mmol/l) and calcium >9.5 mg/dl (>2.37 mmol/l) — No phosphate binder is necessary in most patients.
- Phosphate >5.5 mg/dl (>1.78 mmol/l) and calcium >9.5 mg/dl (>2.37 mmol/L) — We recommend the administration of a non-calcium containing phosphate binder rather than calcium containing binders. Either sevelamer or lanthanum can be given.
- Phosphate >5.5 mg/dl (>1.78 mmol/l) and calcium <9.5 mg/dl (<2.37 mmol/l) — First titrating a calcium-based phosphate binder (up to 1,500 mg of elemental calcium from binders alone if there is concurrent use of active vitamin D analogues). If phosphate remains above 5.5 mg/dl (>1.78 mmol/l), then add a non-calcium containing phosphate binder.

Step 3. The next step is to decide whether phosphate binder therapy is sufficient or whether a calcimimetic or vitamin D analogue should be added. This is based upon calcium, phosphate, and PTH levels that are measured when administering optimal phosphate binder therapy (as defined in step 2).

If calcium supplementation and phosphate binders are effective in controlling PTH (ie, level between 150 and 300 pg/ml), no additional therapy may be needed. Serial follow up of PTH levels should be performed at three month intervals to assess the continued control of disease.

If PTH levels remain greater than 300 pg/ml with optimal binder therapy, the choice is either cinacalcet or vitamin D analogues. The decision to use vitamin D or cinacalcet as the next step, without additional data on outcomes, should be based upon the calcium and phosphate levels that are measured when administering optimal phosphate binders:

If the calcium and phosphate levels are both toward the upper limit of target levels, we suggest administering cinacalcet. This is because cinacalcet lowers both these parameters, while vitamin D therapy has the potential to further increase calcium and phosphorus levels.

If the calcium level is near or below the lower limit of normal and the phosphate is well within the normal range, we suggest the administration of vitamin D, given that cinacalcet would further lower the serum calcium. There are no compelling data to use intravenous versus oral therapy or one form of vitamin D analogue over the other. Cost and patient compliance would be two considerations.

Based upon this rationale, we initiate cinacalcet in patients with PTH >300 pg/ml and the following measured levels of phosphate and calcium when administering optimal phosphate binder therapy:

- Phosphate >5.5 mg/dl (>1.78 mmol/l) and Calcium >8.4 mg/dl (>2.1 mmol/l)
- Phosphate <5.5 mg/dl (<1.78 mmol/l) and Calcium >9.5 mg/dl (>2.37 mmol/l)

Since cinacalcet lowers serum calcium levels, it should not be initiated if the serum calcium level is less than 8.4 mg/dl (less than 2.1 mmol/l).

We suggest that a vitamin D analogue would be the initial choice in patients with PTH >300 pg/ml, and the following measured levels of phosphate and calcium when administering optimal phosphate binder therapy:

- Phosphate <5.5 mg/dl (<1.78 mmol/l) and Calcium <9.5 mg/dl (<2.37 mmol/l)

Since vitamin D analogues raise serum calcium and phosphate levels, we recommend NOT initiating these agents if the serum calcium level is greater than 9.5 mg/dl (>2.37 mmol/l), serum phosphate is greater than 5.5 mg/dl (>1.78 mmol/l), or the Ca X P product is greater than 55 mg^2/dl^2.

Step 4. The final step is to adjust the doses of phosphate binders, active vitamin D, and cinacalcet to attempt to attain target values:

Among patients with inadequate reduction of PTH with initial therapies, serum phosphate <5.5 mg/dl (<1.78 mmol/l), and serum calcium <9.5 mg/dL (<2.37 mmol/l), we suggest adding active vitamin D among those already receiving cenacle

Among patients with inadequate reduction of PTH with initial therapies and serum calcium >8.4 mg/dl (>2.1 mmol/l), we suggest adding cinacalcet among those already receiving a vitamin D analogue.

10. Preparation for and initiation of renal replacement therapy

It is important to identify patients who may eventually require renal replacement therapy since adequate preparation can decrease morbidity and perhaps mortality. Early identification enables dialysis to be initiated at the optimal time with a functioning chronic access and may also permit the recruitment and evaluation of family members for the placement of a renal allograft prior to the need for dialysis. In addition, the ability of the individual to psychologically accept the requirement of life-long renal replacement therapy is often diminished if inadequate time has elapsed between the time of recognition of ESRD and the initiation of dialysis.

CKD progresses at a variable rate due to differences in the clinical course of the underlying diseases (particularly between individuals) and the recognition that the natural history of progressive renal disease can be altered by various therapeutic interventions, particularly strict blood pressure control with an ACE inhibitor or ARB. As a result, exactly if and when a patient may require dialysis or renal transplantation is unclear. In addition, some patients refuse renal replacement therapy until the onset of absolute indications, while others desire early initiation to avoid the complications of severe chronic kidney disease, such as malnutrition.

10.1 Referral to nephrologists

Patients with CKD should be referred to a nephrologist early in the course of their disease, preferably before the plasma creatinine concentration exceeds 1.2 (106 micromol/l) and 1.5 mg/dl (133 micromol/l) in women and men, respectively, or the eGFR is less than 60 ml/min per 1.73 m². These subspecialists are trained to help counsel the patient in choosing the optimal renal replacement therapy and to manage the many issues associated with CKD. Lower costs and/or decreased morbidity and mortality may be associated with early referral and care by subspecialists. Reasons for later referral may include disease specific factors, patient and physician dependent causes, and health care system related factors. Late referral to a nephrologist has been associated with higher mortality after the initiation of dialysis (Kazmi et al., 2004).

An equally important component of early identification is institution of renoprotective therapy (eg, ACE inhibitor, angiotensin II receptor blocker, and rigorous blood pressure control) as early as possible after identifying the presence of progressive chronic kidney disease. Protective therapy has the greatest impact if it is initiated before the plasma creatinine concentration exceeds 1.2 (106 micromol/l) and 1.5 mg/dl (133 micromol/l) in women and men, respectively, or the eGFR is less than 60 ml/min per 1.73m². At this point, most patients have already lost more than one-half of their GFR. Waiting until the disease progresses further diminishes the likelihood of a successful response but still should be attempted.

10.2 Choice of renal replacement therapy

Once it is determined that renal replacement therapy will eventually be required, the patient should be counseled to consider the advantages and disadvantages of hemodialysis (in-center or at home), peritoneal dialysis (continuous or intermittent modalities), and renal transplantation (living or deceased donor). The 2006 K/DOQI guidelines recommend that patients with a GFR less than 30 ml/min per 1.73 m² should be educated concerning these issues.

Kidney transplantation is the treatment of choice for ESRD. A successful kidney transplant improves the quality of life and reduces the mortality risk for most patients, when compared with maintenance dialysis. To facilitate early transplantation, a 2008 NKF/KDOQI conference suggested early education and referral to a transplantation center plus the identification of potential living donors.

However, not all patients are appropriate candidates for a kidney allograft because of absolute and/or relative contraindications to this procedure or the subsequent required medications. Referral to a transplant program should occur once renal replacement therapy is thought to be required within the next year.

For these individuals and for those who are suitable transplant recipients but must wait for an available kidney, the choice between hemodialysis or peritoneal dialysis is influenced by a number of considerations such as availability, convenience, comorbid conditions, home situation, age, gender, and the ability to tolerate volume shifts.

In the United States, the universal availability of renal replacement therapy forces the nephrologist to consider its application in every patient in whom it might be indicated. However, the patient, particularly the elderly and terminally ill, may refuse dialysis, a choice which is assuming more prominence as patients and physicians grapple with the increasing use of advance directives, and the laudable goals of death with dignity and life with quality. Nevertheless, not all nephrologists are willing to recommend no treatment, especially when dialysis facilities are available with no need to ration therapy. These issues can be a source of conflict among physicians, patients, and their families.

10.3 Indications for renal replacement therapy

The decision to initiate dialysis in a patient with CKD involves the consideration of subjective and objective parameters by the physician and the patient. These parameters are often modulated by the patient's perception of his or her quality of life and by possible anxiety about starting new therapy that is technologically complex.

There are a number of clinical indications to initiate dialysis in patients with CKD. These include:

- Pericarditis or pleuritis (urgent indication)
- Progressive uremic encephalopathy or neuropathy, with signs such as confusion, asterixis, myoclonus, wrist or foot drop, or, in severe, cases, seizures (urgent indication)
- A clinically significant bleeding diathesis attributable to uremia (urgent indication)
- Fluid overload refractory to diuretics
- Hypertension poorly responsive to antihypertensive medications
- Persistent metabolic disturbances that are refractory to medical therapy. These include hyperkalemia, metabolic acidosis, hypercalcemia, hypocalcemia, and hyperphosphatemia.
- Persistent nausea and vomiting
- Weight loss or signs of malnutrition

However, these indications are potentially life-threatening. They occur when the patient has very advanced CKD, such as may be observed in those who present with severe uremia and have not had prior medical contact. For patients under medical care, delaying initiation of dialysis until one or more of these complications is present may put the patient at unnecessary jeopardy; dialysis should therefore be initiated well before these indications have developed. Patients with CKD should, therefore be closely followed and the GFR estimated.

11. Cardiovascular disease in patients with chronic kidney disease

11.1 Introduction

Cardiovascular disease (CVD) is common in the general population, affecting the majority of adults past the age of 60 years. The prevalence of coronary heart disease (CHD) is approximately one-third to one-half that of total CVD.

It is increasingly appreciated that chronic renal dysfunction alone is an independent risk factor for the development of CHD, and for more severe coronary heart disease (CHD)

(USRDS, 2010). Chronic kidney disease (CKD) is also associated with an adverse effect on prognosis from cardiovascular disease. This includes increased mortality after an acute coronary syndrome and after percutaneous coronary intervention (PCI) with or without stenting.

Patients on renal replacement therapy appears to be at extraordinary risk for premature death due to cardiovascular complications. Although accelerated atherosclerosis may be one important cause of the high cardiovascular mortality in this patient group, the CVD pattern is atypical in that volume overload and left ventricular hypertrophy (LVH) are very common. In addition, the incidence of sudden cardiac death, arrhythmias, hypertension, coronary artery disease (CAD), peripheral vascular disease (PVD), and pericarditis is markedly increased, and cardiac arrest or arrhythmia is the major cause of cardiovascular death in this patient population. CKD patients should therefore be considered in the "highest-risk" group for CVD, irrespective of levels of traditional CVD risk factor. The presence of cardiovascular disease is an important predictor of mortality in patients with ESRD, as it accounts for almost 50 percent of deaths. Of these, approximately 20 percent can be attributed to the consequences of CAD. Patients with varying stages of CKD but who are not yet dialysis-dependent also have a markedly increased risk of morbidity and mortality from CVD, including CHD.

11.2 Epidemiology

The incidence/prevalence of coronary disease in the dialysis population depends in part upon the definition that is used (Herzog, 2003). A confounding issue is that coronary disease often presents in atypical fashion in dialysis patients. As a result, the presence of CHD is frequently overlooked due to the absence of classic symptoms and/or signs of heart disease. Overall, the incidence is much higher than that observed in the general population.

Approximately 40 percent of incident dialysis patients have ischemic heart disease (Cheung et al., 2004), with an annual rate of myocardial infarction and/or angina of approximately 10 percent.

- Almost 40 percent of the 1846 patients enrolled in the HEMO report were noted to have ischemic heart disease at study initiation (Cheung et al., 2004). During the mean follow-up period of 2.8 years, angina and acute myocardial infarction were responsible for 43 percent of all cardiac hospitalizations, with ischemic heart disease causing 62 percent.
- Utilizing data from Wave II of the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality study, the incidence of an acute coronary syndrome was 2.9 percent per year among 3374 incident dialysis patients followed for approximately two years (Trespalacios et al., 2002).
- In one Japanese study, the presence of significant occult coronary artery disease using coronary angiography (greater than 50 percent stenosis) was found in 16 of 30 asymptomatic patients (53 percent) initiating renal replacement therapy (Ohtake et al., 2005).

Cardiac disease, including coronary artery disease, left ventricular hypertrophy (LVH) and heart failure (HF), is common in patients with chronic kidney disease (CKD). LVH appears to be increasingly prevalent as the glomerular filtration rate (GFR) declines and with increased dialysis vintage.

- LVH has been found in as many as 30 to 45 percent of patients with chronic kidney disease (CKD) not yet on dialysis, with a higher prevalence and more severe LVH in those with increasingly lower degrees of renal function (Moran et al., 2008).

- Concentric LVH has been documented by echocardiography in 42 percent of patients at the start of dialysis and in as many as 75 percent of patients who have been on hemodialysis for 10 years (Parfrey & Foley, 1999).

11.3 Association with traditional and non-traditional risk factors

Although CKD alone is an independent risk factor for CHD, it is worthwhile to review the variety of abnormalities commonly observed in these patients that enhance the overall risk of cardiovascular disease (Table 4).

Traditional cardiovascular risk factors, such as hypertension (which may be accompanied by left ventricular hypertrophy), smoking history, diabetes, dyslipidemia and older age, are highly prevalent in CKD populations. The number of cardiovascular risk factors appears to correlate with the severity of kidney dysfunction.

Patients with CKD are also more likely to have the metabolic syndrome, which could contribute to the increase in cardiovascular risk (Chen et al., 2004). This syndrome is defined as some combination of insulin resistance, dyslipidemia, elevated serum glucose, abdominal obesity, and hypertension.

There are additional possible risk factors that are relatively unique to patients with moderate to severe CKD. These include retention of uremic toxins, anemia, increased calcium intake, abnormalities in bone mineral metabolism, proteinuria, and/or an "increased inflammatory-poor nutrition" state.

The purported link between some of these additional factors and an enhanced risk for CHD is uncertain. As an example, studies examining the relationship between coronary artery calcification and abnormalities in mineral metabolism (phosphorus, calcium, and parathyroid hormone) in patients with moderate to severe CKD have demonstrated increased coronary artery calcification, but conflicting data on independent risk factors (Dellegrottaglie et al., 2006).

Traditional CVD Risk Factors	CKD Related "Nontraditional" CVD Risk Factors
Older age	Type (diagnosis) of CKD
Male gender	Decreased GFR
White Race	Proteinuria
Hypertension	Renin-angiotensin system activity
Elevated LDL cholesterol	Extra-cellular fluid volume overload
Decreased HDL cholesterol	Abnormal Calciam and Phosphorus
Diabetes mellitus	Metabolism
Tobacco use	Dyslipidemia
Physical inactivity	Anemia
Menopause	Malnutrition
Psychosocial stress	Inflammation
Family history of CVD	Infection
	Thrombogenic fectors
	Oxidative stress
	Elevated homocysteine
	Advanced glycation end-products (AGEs)
	Uremic toxins

Table 4. Traditional vs. CKD- related factors associated with an increased risk for CVD.

Elevated levels of CRP and asymmetric dimethylarginine were both associated with increased risks of all cause and cardiovascular mortality in the Modification of Diet in Renal Disease study, after adjustment for known cardiovascular risk factors (Menon et al., 2005; Young et al., 2009), though a similar relationship for CRP was not seen in the Irbesartan for Diabetic Nephropathy trial. Hyperhomocysteinemia has also been inconsistently associated with increased cardiovascular risk.

Anemia has emerged as an important, independent risk factor for the development and progression of LVH and HF in CKD, and of adverse cardiovascular outcomes, including mortality. The presence of LVH is important clinically because it is associated with increases in the incidence of heart failure, ventricular arrhythmias, death following myocardial infarction, decreased LV ejection fraction, sudden cardiac death, aortic root dilation, and a cerebrovascular event.

11.3.1 Inflammation

The chronic inflammatory milieu of uremia may contribute to vascular calcification. A large number of proinflammatory or antiinflammatory substances have been evaluated as possible factors underlying this abnormal milieu. These include osteopontin, osteoprotegerin and fetuin. Osteopontin (a chemoattractant) concentrations in blood and in atherosclerotic plaques are increased in hemodialysis patients compared to age-matched healthy controls, and may correlate with aortic calcification score.

Inflammatory states and chronic kidney disease are also associated with altered levels of osteoprotegerin and alpha-2-Heremann Schmitt glycoprotein (AHSG, or human fetuin). Both of these factors are considered protective against extraosseous calcification.

Normal levels of fetuin help clear apoptotic cells, which act as potential niduses for crystal formation in medial arterial calcification, by augmenting phagocytosis. In vitro, fetuin appears to inhibit the precipitation of hydroxyapatite from supersaturated solutions of calcium and phosphate via the formation of a fetuin-mineral complex (FMC), which contains calcium phosphate, matrix Gla protein (MGP), fetuin, and other fetuin-like compounds.

Low fetuin levels, which are observed with CKD and other chronic inflammatory states, are associated with increased vascular calcification, cardiovascular mortality, and overall mortality in some studies of dialysis patients. The sera of dialysis patients with low fetuin concentrations also demonstrated impaired capacity to inhibit calcium/phosphate precipitation.

11.3.2 Oxidative and carbonyl stress

Increased production of cytokines due to oxidative stress is also observed among patients with renal failure. Oxidative stress, which occurs when there is an excessive free-radical production or low antioxidant level, could be an important condition for the development of endothelial dysfunction, inflammation, and atherogenesis. Lower plasmalogen levels, an indicator of such stress, have been reported in malnourished and inflamed patients with CKD.

With renal failure, molecules that are not cytokines may also accumulate and provoke an inflammatory response. As an example, advanced glycosylated end-products (AGE), which result from carbonyl stress, can clearly initiate inflammation in patients with renal failure.

11.3.3 Decreased antioxidants

The oral intake or the level of some antioxidants is lower than normal in both CRF and ESRD patients. An acute-phase response is also associated with decreased plasma levels of several antioxidants, such as serum vitamin C concentrations. Low serum vitamin C levels are in turn associated with increased cardiovascular morbidity and mortality.

11.3.4 Vascular calcification

Vascular calcification in patients with CKD, noted radiologically for decades, has been of increasing interest within the renal literature. The presence of calcium in the intimal layer may be a marker for plaque vulnerable to rupture and is associated with occlusive disease, while the presence of calcium in the vessel media may have direct adverse effect on vascular distensibility. The reduced vascular compliance may lead to increased pulse pressure, reduced coronary perfusion, and abnormal autonomic and endothelial vasomotor function. Such overall vascular stiffness may have a profound negative effect upon survival for dialysis patients. Risk factors to both types of calcification include excess calcium and phosphate, hyperparathyroidism/chronic inflammation and decreased circulating, or tissue-bound, inhibitors of the calcification process. Both appear to progress by a series of elaborate mechanisms similar to bony ossification and may involve genetic susceptibility or gene polymorphisms.

11.3.5 Chronic kidney disease alone as a risk factor for CHD

Based upon observational data in patients with CKD due to a variety of systemic and kidney-specific diseases, CKD is associated with an increased risk of adverse cardiovascular outcomes and is considered a CHD risk equivalent and the risk increases with increasing renal dysfunction and/or severity of proteinuria. The presence of both decreased renal function and increased proteinuria appears to further enhance the risk of cardiovascular disease versus that associated with either alone.

All patients with the same degree of renal dysfunction also do not have the same risk of cardiovascular disease. As an example, the overall risk for a 25 year old nonsmoking man with moderate CKD due to IgA nephropathy is not the same as that of a 65 year old man with a similar degree of CKD due to IgA but with a long history of smoking, hypertension, and elevated serum cholesterol levels. Thus, in addition to the evaluation for the presence of CKD, the proper assessment of overall cardiovascular risk requires an adequate assessment for the presence and severity of the other major risk factors for cardiovascular disease. Therefore, patients with either an estimated GFR that is less than 60 ml/min per 1.73 m^2 or with proteinuria greater than one gram/day to have sufficient increased cardiovascular risk to be considered a CHD risk equivalent.

11.4 Treatment and prevention of cardiovascular disease
11.4.1 Therapeutic lifestyle changes

Therapeutic lifestyle changes are a part of decreasing the risk of adverse cardiovascular outcomes in patients with CKD.

11.4.2 Smoking

In hemodialysis patients, smoking greatly increases the risk for cardiovascular morbidity and mortality. However, unlike that found in the general population, there are no studies

showing beneficial cardiovascular outcomes with smoking cessation in dialysis patients. Despite this, we recommend that dialysis patients completely stop smoking, given the marked benefits of smoking cessation observed in the general population.

11.4.3 Weight reduction

In those with normal renal function, obesity is associated with an increased risk for cardiovascular disease. By comparison, the benefits of weight reduction in dialysis patients are unclear. In contrast, there appears to be a survival advantage in obese dialysis patients. The higher mortality risks in dialysis patients with lower body mass indices may be attributed to malnutrition. Limited data suggest that increased muscle mass confers greater survival advantage than increased fat in the dialysis population. In general, we do not currently recommend weight reduction for dialysis patients, although it is reasonable to recommend an increase in muscle rather than fat. Weight reduction may be attempted in morbidly obese patients.

11.4.4 Exercise

Regular exercise has a variety of possible cardiovascular benefits in those with normal renal function. By comparison, a paucity of data exists concerning the association between cardiovascular benefits, survival, and exercise in dialysis patients. This was examined using data for 2507 patients from the Dialysis Morbidity and Mortality Wave 2 study. Decreased mortality was associated with patients who exercised two to three and four to five times per week. However, for unclear reasons, daily exercise provided no survival benefit.

11.4.5 Oxidative stress

A number of studies have demonstrated that hemodialysis patients are, in general, at a state of increased oxidative stress, suggesting the possibility that antioxidant therapies may improve clinical outcomes. Limited evidence suggests that an attempt to lower oxidative stress may improve cardiovascular disease outcomes in ESRD.

11.4.6 Hyperhomocysteinemia

Hyperhomocysteinemia is common in patients with ESRD. As observed in those with normal kidney function, lowering homocysteine levels does not improve cardiovascular outcomes in dialysis patients. Folic acid and B vitamins decrease homocysteine levels in this population .Treatment with high doses of folic acid and B vitamins did not improve survival or reduce the incidence of vascular disease in patients with advanced CKD or ESRD. This was best shown in the double-blind randomized controlled trial Homocysteinemia in Kidney and End Stage Renal Disease (HOST), which compared the effect of folic acid (40 mg/day), pyridoxine (100 mg/day), and vitamin B12 (2 mg/day) versus placebo on vascular outcomes in 2056 patients with advanced CKD, including ESRD. At a median follow-up of 3.2 years, there was NO difference between the groups in terms of total mortality, myocardial infarction, stroke, and amputations.

11.4.7 Mineral metabolism issues

Cardiovascular disease in dialysis patients may be due in part to the presence of excess vascular calcification, particularly in the form of extensive coronary artery calcification. A key question is what drives the development and maintenance, or progression, of such abnormal calcification. Abnormalities of mineral metabolism and therapeutic maneuvers

aimed at correcting these abnormalities have been implicated as primary underlying pathogenic factors. These include hyperphosphatemia, administration of calcium-containing oral phosphate binders, elevated parathyroid hormone levels, and (possibly) decreased serum vitamin D levels.

No prospective randomized studies have demonstrated a cardiovascular benefit and/or a survival advantage with any of the current therapeutic options, including limiting calcium intake, use of non-calcium or calcium-containing phosphate binders, active vitamin D therapy, and administration of calcimimetics. However, observational studies have shown improved survival in hemodialysis patients treated with active vitamin D analogues. Despite the absence of evidence from randomized trials, we generally aim for a calcium x phosphate product less than 55 mg^2/dL^2 using current therapeutic options. However, it is possible that even lower levels (<50 mg^2/dl^2) offer further survival advantage.

11.4.8 Diabetes mellitus

Guidelines from the American Heart Association and the American Diabetes Association recommended optional glycemic control, reaching blood pressure target levels and lipids monitoring (with subsequent dysplipidemia treatment). In CKD patients with diabetes, CVD must be treated aggressively.

11.4.9 Anemia

Because anemia is contributing to the development of LVH in ESRD and partial correction of severe anemia with epoetin results in regression of LVH , epoetin treatment is advocated . Treatment of severe anemia is also associated with less ischemic symptoms in patient with CAD. However, although life quality improves after anemia correction; the evidence that epoetin treatment reduces cardiovascular mortality in ESRD is based on data from observational studies only.

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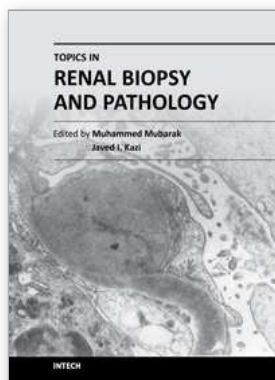
Topics in Renal Biopsy and Pathology
Edited by Dr. Muhammed Mubarak

There is no dearth of high-quality books on renal biopsy and pathology in the market. These are either single author or multi-author books, written by world authorities in their respective areas, mostly from the developed world. The vast scholarly potential of authors in the developing countries remains underutilized. Most of the books share the classical monotony of the topics or subjects covered in the book. The current book is a unique adventure in that it bears a truly international outlook and incorporates a variety of topics, which make the book a very interesting project. The authors of the present book hail not only from the developed world, but also many developing countries. The authors belong not only to US but also to Europe as well as to Pakistan and Japan. The scientific content of the book is equally varied, spanning the spectrum of technical issues of biopsy procurement, to pathological examination, to individual disease entities, renal graft pathology, pathophysiology of renal disorders, to practice guidelines.

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