Introduction

There is a greater prevalence of anemia of chronic kidney disease in those older than 60 years This is probably secondary to the greater rate of chronic kidney disease in older individuals, as well as the lower estimated glomerular filtration rates (GFRs) that are associated with aging ***(Lerma, 2014).***

The morbidity and mortality depend greatly on the underlying etiology of the patient's anemia as well as the stage of the disease, whether early or advanced. In fact, in individuals with advanced stages of chronic kidney disease, the etiology of anemia tends to be multifactorial (eg, decreased RBC production due to lack of erythropoietin, increased RBC destruction due to hemolysis [intravascular or extravascular], as well as increased blood loss due to multiple venipunctures for an array of indications) ***(Robert et al., 2014).***

Earlier treatment of anemia of CKD may reduce mortality during first year of dialysis ***(Xue et. al. 2002).***

In the presence of anemia, renal damage was more severe: Serum creatinine level was higher in patients with anemia compared with those without anemia and GFR was significantly lower in patients with anemia compared with those without anemia ***(Daniela et al., 2012).***

Anemia is strongly predictive of complications and death from cardiovascular causes in patients with chronic kidney disease (CKD) ***(Winerde et al., 2005).***

Also a correlation between survival and Hb concentration has been established in large retrospective studies ***(Clliwet al., 2002).***

The national Kidney foundation Kidney dialysis outcome quality initiative (NKF. K/DOQI) suggest that the target hemoglobin level in chronic kidney disease patients should be between 11-12 gm/dL. Treatment for Anemia of chronic kidney disease (CKD) should start when hemoglobin falls to less than 11 gm/dL ***(Locatelli et al., 2004).***

Aim of the Work

This study will be carried out to assess of microcytic anemia among regular Hemodialysis patients and its possible causes and compression between microcytic and non microcytic anemia.

Chapter (I): Choric Kidney Disease

Definition of Choric Kidney Disease:

According to Kidney Disease Outcome Quality Initiative (KDOQI) chronic kidney disease (CKD) is defined as Kidney damage for 3 months due to structural of functional abnormalities of the kidney, with or without decreased Glomerular filtration rate (GFR), manifest by either:

- Pathological abnormalities.
- Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests.
- In general it can be difined as GFR <60 mL/min/1.73m2 for 3 months, with or without kidney damage ***(Astor et al., 2012).***

According to National Institute for Health and Care Excellence (NICE) clinical guidelines 2014 CKD describes abnormal kidney function and/or structure. It is common, frequently unrecognised and often exists together with other conditions (such as cardiovascular disease and diabetes). Moderate to severe CKD is also associated with an increased risk of other significant adverse outcomes such as acute kidney injury, falls, frailty and mortality. The risk of developing CKD increases with age. As kidney dysfunction progresses, some coexisting conditions become more common and increase in severity ***(D'Souza et al., 2014).***

CKD is a progressive condition marked by deteriorating kidney function over time. Typically kidney function is quantified by glomerular filtration rate (GFR) most frequently estimated using equations that incorporate serum creatinine along with demographic data ***(Steven et al., 2006).***

Staging of CKD

According to **KIDGO 2012**, CKD is classified based on cause, albuminuria and GFR.

1. Staging of CKD according to Albuminuria as seen in table (1) for example nephrotic syndrome is considered stage A3 (albumin excretion usually 42200 mg/24 hours [ACR 42220 mg/g; 4220 mg/mmol]).

Table (1): Shows the stages of CKD according to albuminuria.

Category	AER(mg/24 hours)	ACR (mg/mmol)	ACR (mg/g)	Terms
A1	Less than 30	Less than 3	Less than 30	Normal and mildly increased
A2	30-300	3-30	30-300	Moderately increased
A3	More than 300	More than 30	More than 300	Severely increased

Abbreviations: AER, albumin excretion rate
ACR: albumin-to-creatinine ratio
CKD: chronic kidney disease

2. Staging of CKD according to GFR (ml/min/1.73 m2).

Table (2): Shows the stages of CKD according to GFR

GFR category	GFR (ml/min/1.73 m2)	Terms
G 1	More than 90	Normal or high
G 2	60-89	Mildly decreased
G 3a	45-59	Mildly to moderately decreased
G 3b	30-44	Moderately to severely decreased
G 4	15-29	severely decreased
G 5	Less than 15	Kidney failure

Abbreviations: CKD: chronic kidney disease.
GFR: glomerular filtration rate.

(Astor et al., 2012)

The staging of CKD is advantageous for many reasons. Having a common classification scheme will facilitate defining the epidemilogy of CKD and its complications in the population. This classification will provide a common language for patients and the practitioners involved in the clinical care and research of CKD. The system also provides a framework action plan for management ***(Astor et al., 2012).***

Causes of CKD *(Kumar et al., 2011)*

1. Congenital and inherited disease

- **Polycystic kidney disease** (adult and infantile forms): Is an inherited kidney disorder. It causes fluid-filled cysts to form in the kidneys and may cause kidney failure.

- **Medullary cystic disease**: An inherited condition in which cysts in the center of each kidney cause the kidneys to gradually lose their ability to work.
- **Tuberous sclerosis**: Is a rare multi-system genetic disease causes benign tumors to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin.
- **Oxalosis:** Is a rare metabolic disorder that occurs when the kidneys stop eliminating calcium oxalate crystals from the body through the urine. Because the kidneys stop functioning, oxalate crystals are deposited elsewhere in the body.
- **Cystinosis:** is a lysosomal storage disease characterized by accumulation of cystine. Cystinosis is the most common cause of Fanconi syndrome in children. Which occurs when the function of renal tubules are impaired.
- **Congenital obstructive uropathy:** It can be caused by a lesion at any point in the urinary tract like posterior urethral valves, urolithiasis, and ureteral herniation.

2. Glomerular disease

Primary glomerulonephritides including:

- **Focal glomerulosclerosis**: is the most common causes of primary glomerular diseases in adults. The condition causes asymptomatic proteinuria or

nephrotic syndrome with or without renal insufficiency. Generally, FSGS is a progressive form of kidney disease, accounting for 2.3% of patients with end-stage renal disease (ESRD).

Secondary glomerular disease

- **Systemic lupus erythematosus (SLE):** Is a chronic inflammatory disease may affect kidneys (lupus nephritis) and than 90% of cases of SLE occur in women, frequently starting at childbearing age.
- **Polyangiitis:** Is vasculitis of small vessels like polyarteritis nodosa (PAN) which is necrotizing inflammatory lesions that affect medium-sized and small muscular arteries.
- **Wegener's granulomatosis:** Is autoimmune disease cause vasculitis of small and medium sized vessels and cause rapidly progressive glomerulonephritis leading to chronic kidney failure.
- **Amyloidosis:** Is accumulation of amyliod which become insoluble and deposit in organs or tissues, disrupting normal function leading to ESRD.
- **Diabetic glomerulosclerosis:** Is a progressive kidney disease caused by damage to the capillaries in the kidney's glomeruli. It is characterized by nephrotic syndrome and diffuse scarring of the glomeruli. It is due to longstanding diabetes mellitus.

- **Accelerated hypertension:** is hypertensive emergency in which elevated blood pressure results in target organ damage as brain and kidneys.
- **Haemolytic uraemic syndrome:** Is a clinical syndrome characterized by progressive renal failure that is associated with microangiopathic (nonimmune, Coombs-negative) hemolytic anemia and thrombocytopenia. HUS is the most common cause of acute kidney injury in children and is increasingly recognized in adults**.**
- **Thrombotic thrombocytopenic purpura:** Is a rare blood disorder characterized by clotting in small blood vessels of the body (thromboses), resulting in a low platelet count. The disease consists of the pentad of microangiopathic hemolytic anemia, thrombo-cytopenic purpura, neurologic abnormalities, fever, and renal disease.
- **Systemic sclerosis:** Is a systemic connective tissue disease. Characteristics of systemic sclerosis include essential vasomotor disturbances; fibrosis; subsequent atrophy of the skin, subcutaneous tissue, muscles, and internal organs (eg, alimentary tract, lungs, heart, kidney, CNS); and immunologic disturbances accompany these findings.
- **Sickle cell disease:** Is genetic disorders resulting from the presence of a mutation of hemoglobin cause anemia and hypertension and protienurea and renal failure.

3. Vascular disease

- **Hypertensive nephrosclerosis:** Commn in black Africans renal failure occurs as complication of longstanding hypertension.
- **Reno-vascular disease:** Is a progressive condition that causes narrowing or blockage of the renal arteries or veins. These are the blood vessels that take blood to and from the kidneys.
- **Small and medium-sized vessel vasculitis**: Like Polyangiitis and Wegener's granulomatosis.

4. Tubulointerstitial disease

- **Tubulointerstitial nephritis:** Is a form of nephritis affecting the interstitium of the kidneys surrounding thetubules. This disease can be either acute, meaning it occurs suddenly, or chronic, meaning it is ongoing and eventually ends in kidney failure.
- Idiopathic due to drugs **(nephrotoxic analgesics):** The analgesics induce renal papillary necrosis and chronic interstitial nephritis. They appear to result from decreased blood flow to the kidney, rapid consumption of antioxidants, and subsequent oxidative damage to the kidney. This kidney damage may lead to progressive chronic kidney failure.
- **Immunologically Mediated:** Like SLE and Rheumatoid Arthritis

- **Reflux nephropathy:** Vesicoureteral reflux is characterized by the retrograde flow of urine from the bladder to the kidneys. And may be associated with urinary tract infection (UTI), hydronephrosis, and abnormal kidney development (renal dysplasia).
- **Tuberculosis:** Is chronic systemic inflammation may affect genitourinary system lead to Flank pain, Dysuria, Frequent urination in men, a painful scrotal mass, prostatitis, orchitis, or epididymitis, In women, symptoms mimicking pelvic inflammatory disease and finally ESRD.
- **Schistosomiasis:** A parasitic disease caused by Schistosoma and consider the main cause of cancer baldder and this lead to ESRD.
- **Nephrocalcinosis:** Is increasing of calcium levels in the kidneys Most often, the increase in renal calcium is generalized, as opposed to the localized increase observed in calcified renal infarct and caseating granulomas of renal tuberculosis.
- **Multiple myeloma (myeloma kidney):** Is a debilitating malignancy can range from asymptomatic to severely symptomatic, with complications requiring emergent treatment. Systemic ailments include bleeding, infection, and renal failure; pathologic fractures and spinal cord compression.

- **Balkan nephropathy:** Is a chronic tubulointerstitial disease associated with a high frequency of urothelial atypia, occasionally culminating in tumors of the renal pelvis and urethra.
- **Renal papillary necrosis (diabetes, sickle cell disease and, trait, analgesic nephropathy)**
- **Chinese herb nephropathy:** Is a rapidly progressive interstitial nephropathy reported after the introduction of Chinese herbs in a slimming regimen followed by young Belgian women.

5. Urinary tract obstruction

- **Calculus disease:** Obstruction due to stone lead to recurrent infection and hydronephrosis
- **Prostatic disease:** Mainly in old men lead to recurrent infection and hydronephrosis
- **Pelvic tumors:** Like cancer ovary or uterus may cause unilateral or bilateral ureteric compression.
- **Retroperitoneal fibrosis:** May cause unilateral or bilateral ureteric compression.
- **Schistosomiasis:** The ova may act as stone.

(Kumar et al., 2011)

Risk Factors for CKD

Table (3): Risk Factors for Chronic Kidney Disease and Its Outcomes.

Type	Definition	Example
Susceptibility factors	Factors that increase susceptibility to kidney damage	Older age, family history of chronic kidney disease, reduction in kidney mass, low birth weight, minority status, low income or educational level
Initiation factors	Factors that directly initiate kidney damage	Diabetes mellitus, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, obstruction of lower urinary tract, drug toxicity
Progression factors	Factors that cause worsening kidney damage and faster decline in kidney function after kidney damage has started	Higher level of proteinuria, higher blood pressure level, poor glycemic control in diabetes, smoking
End-stage factors	Factors that increase morbidity and mortality in kidney failure	Lower dialysis dose (Kt/V), *temporary vascular access, anemia, low serum albumin level, late referral for dialysis

Kt/V is the accepted nomenclature for dialysis dose, "K" represents urea clearance, "t" represents time, and "V" represents volume of distribution for urea.

The risk of developing CKD as seen in table (3) is increased in some patients without kidney damage and with a normal or elevated GFR. During the routine health care visit, all patients should be assessed for increased risk based on clinical and sociodemographic factors. Patients determined to be at increased risk for kidney disease should undergo testing for markers of kidney damage and an

estimation of their GFR. Patients found to have chronic kidney disease should be evaluated and treated as specified in National Kidney Foundation (NKF) guidelines ***(Johnson et al., 2004).***

Pathophysiology of CKD

The pathophysiology of CKD involves initiating mechanisms specific to the underlying etiology as well as a set of progressive mechanisms that are a common consequence following long-term reduction of renal mass, irrespective of etiology. Such reduction of renal mass causes structural and functional hypertrophy of surviving nephrons. This compensatory hypertrophy is mediated by vasoactive molecules, cytokines, and growth factors and is due initially to adaptive hyperfiltration, in turn mediated by increases in glomerular capillary pressure and flow. Eventually, these short-term adaptations prove maladaptive, in that they predispose to sclerosis of the remaining viable nephron population. Increased intrarenal activity of the renin-angiotensin axis appears to contribute both to the initial adaptive hyperfiltration and to the subsequent maladaptive hypertrophy and sclerosis ***(Harrison et al., 2009).***

Azotemia refers to the retention of nitrogenous waste products as renal insufficiency develops .Uremia refers to the more advanced stages of progressive renal insufficiency when the complex, multiorgan system derangements become clinically manifest as seen in figure (1) ***(Harrison et al., 2009).***

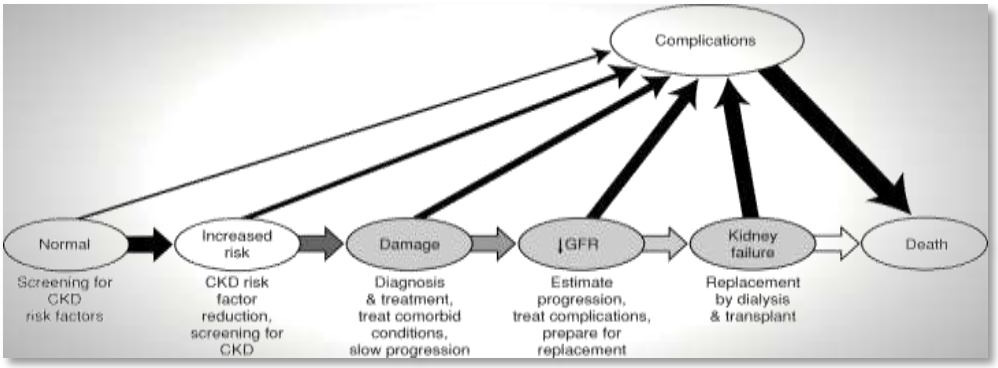

Fig. (1): Complication of CKD ***(Harrison et al., 2009)***

Clinical Picture of CKD

- Malaise, loss of energy
- Loss of appetite
- Insomnia
- Nocturia and polyuria due to impaired concentrating ability
- Itching
- Nausea, vomiting and diarrhea
- Paraesthesiae due to polyneuropathy
- 'Restless legs' syndrome (overwhelming need to frequently alter position of lower limbs)
- Bone pain due to metabolic bone disease
- Paraesthesiae and tetany due to hypocalcaemia
- Symptoms due to salt and water retention – peripheral or pulmonary oedema
- Symptoms due to anaemia