# Introduction

The Kidney Disease Outcome Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) has defined chronic kidney disease (CKD) as either kidney damage or glomerular filtration rate (GFR) of < 60 mL/min/1.73m$^2$ for ≥ 3 months, irrespective of the underlying etiology of the kidney damage. According to the level of GFR, individuals with chronic kidney disease are classified into 5 stages, (stage 1-5), with higher stages representing lower GFR levels. The final stage of CKD (stages 5), known as kidney failure, is defined as GFR ≤ 15 mL/min/1.73m$^2$, or need for initiation of kidney replacement therapy (dialysis or transplantation) for treatment of complications of decreased GFR, which would otherwise increase the risk of mortality and morbidity. Currently, haemodialysis is the main mode of treatment of patients with kidney failure ***(Graves et al., 2008)***.

Chronic kidney disease is a major health problem worldwide. In Egypt, the estimated annual incidence of chronic renal failure (CRF) is around 74 per million populations, and the total prevalence of patients on dialysis is 264 per million populations. This increasing incidence could be explained by the increased prevalence of diabetes and hypertension, the major two risk factors for CKD ***(Ibrahim et al., 2010)***.

Cardiovascular disease, including coronary artery disease (CAD) is the main cause of mortality in CRF patients.

Atherosclerosis is highly prevalent in advanced renal failure, and progresses faster in patients with renal dysfunction than in general population ***(Amann et al., 2004)***. Moreover, chronic inflammation, oxidative stress and endothelial dysfunction, which play an important role in atherothrombosis, are present even in early stages of renal insufficiency ***(Stam et al., 2006)***.

Endothelial dysfunction has been regarded as an early event in the atherosclerotic process ***(Suzuki et al., 2007)*** and has a high predictive value for ischaemic events ***(Migliacci et al., 2007)***. Some plasma biomarkers of inflammation and endothelial dysfunction have been recognized as important cardiovascular risk factors ***(Zoppini et al., 2006)***.

**Cadherin 5** is a single-chain, transmembrane, 140 k Da glycoprotein, belonging to the cadherin family of cell adhesion molecules. Its gene is located in a six-cadherin cluster in a region on the long arm of chromosome 16 ***(Corada et al., 2001).***

**Cadherin 5** has been given the name "vascular endothelial cadherin" (VE-cadherin) because of its selective expression in endothelial cells (ECs) ***(Leckband et al., 2000).*** It is involved in the maintenance of endothelial permeability, in the control of trafficking of leukocytes from blood toward inflamed tissues ***(Elizabeth et al., 2007)*** and in the morphogenic and proliferative events associated with angiogenesis **(*Dejana et al., 2001 and Soeki et al., 2004).***

Researches have proposed cadherin 5 as a specific biomarker of EC dysfunction and as a major determinant of risk of CAD ***(Leroyer et al., 2005 and Nozaki et al., 2009).*** Therefore, measurement of its plasma levels could be potentially useful for risk assessment of endothelial dysfunction and cardiovascular complications in hemodialysis patients.

# Aim of the Work

This study aims to investigate the role of Cadherin 5 as a potential risk marker for coronary artery disease in patients with chronic renal failure on haemodialysis.

# I) Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as the presence of objective kidney damage and/or the presence of glomerular filtration rate of 60 ml/min/1.73 $m^2$ body surface area or less for at least 3 month irrespective of the underlying etiology of the kidney damage ***(Graves et al., 2008)*.**

**A. Incidence of Chronic Kidney Disease:**

Chronic kidney disease is a world-wide public health problem. It is recognized as a common condition that is associated with an increased risk of cardiovascular disease and chronic renal failure (CRF). More than 50 million people world-wide have chronic kidney disease, and more than one million of them are receiving kidney replacement therapy. Early detection may help slow the progression of kidney disease and avoid kidney failure. Most people with chronic kidney disease do not die of kidney failure, they die of heart disease. In fact, heart disease causes 40-50% of all deaths in patients with chronic kidney disease ***(Schoolwerth et al., 2006).***

The epidemiology of end-stage renal disease (ESRD) in Egypt has never been examined on a national scale. Previous reports have shown that unknown causes of ERSD in Egypt have reached 33.6% ***(E.D.T.A., 1987).*** Schistosomiasis, which is considered a common cause of renal failure in Egypt, is the cause of about 30% of chronic renal failure, most of which is due to obstructive uropathy and a small percentage is due to

schistosomal nephritis ***(Barsoum et al., 1996).***The mean age of ESRD in Egypt is lower than that of Latin American countries and much lower than that of the USA. Hypertension is responsible for 28% of cases of ESRD in Egypt. ESRD of unknown etiology is responsible for 16.2% of cases ***(United States Renal Data System, 1997)***.

**B. Pathophysiology of Chronic Kidney Disease**:

Chronic kidney disease occurs in all age groups, including children. Regardless of the underlying cause, CKD is characterized by progressive scarring that ultimately affects all structures of the kidney. The progression of CKD is postulated to result from a self-perpetuating vicious cycle of fibrosis activated after initial injury. Mechanisms of progressive renal damage include systemic and glomerular hypertension, various cytokines and growth factors, with special emphasis on the role of the rennin-angiotensin-aldosterone system (RAAS), podocyte loss, dyslipidemia and proteinuria. Specific mechanisms of tubule-interstitial fibrosis that are not dependent on glomerulosclerosis, and possible underlying predispositions for CKD, such as genetic factors and low nephron number are also suggested ***(Agnes, 2007).***

Approximately one million nephrons are present in each kidney, each contributing to the total GFR. Regardless of the etiology of renal injury, with progressive destruction of nephrons, the kidney has an innate ability to maintain GFR by hyperfiltration and compensatory hypertrophy of the remaining healthy nephrons. This nephron adaptability allows for continued normal clearance of plasma solutes so that substances such as urea and creatinine start to show significant increase in plasma levels only after total GFR has decreased to 50%. When the renal reserve has been exhausted, the plasma creatinine value will approximately double with a 50% reduction in GFR. A rise in plasma creatinine from a baseline value of 0.6 mg\dL to 1.2 mg\dL in a patient, although still within the reference

range, actually represents a loss of 50% of functioning nephron mass. The residual nephron hyperfiltration and hypertrophy, although beneficial for the reasons noted, has been hypothesized to represent a major cause of progressive renal dysfunction. This is believed to occur because of increased glomerular capillary pressure, which damages the capillaries and leads initially to focal and segmental glomerulosclerosis and eventually to global glomerulosclerosis ***(Matyus et al., 2008).***

Factors that may cause progressive renal injury include the following; systemic hypertension, acute insults from nephrotoxins or decreased perfusion, proteinuria, increased renal ammoniagenesis with interstitial injury, hyperlipidemia and hyperphosphatemia with calcium phosphate deposition ***(Polzien, 2007).***

## C. Etiology of Chronic Kidney Disease:

### 1- Diabetic Nephropathy:

Diabetes mellitus is a state of chronic hyperglycemia sufficient to cause long-term damage to specific tissues, notably the retina, kidneys, nerves and arteries. It affects 176 million people world-wide and the World Health Organization (WHO) predicts that the prevalence of diabetes is set to double by 2030. Type 1 diabetes is due to autoimmune destruction of the insulin-secreting cells of pancreatic β-cells. Type 2 diabetes is due to the combination of cellular resistance to insulin and beta cell failure. Tissue lesions are common to both types of diabetes, and chronic hyperglycemia or a closely related

metabolic abnormality is responsible for diabetic complications including diabetic nephropathy ***(Rigalleau et al., 2008).***

Diabetic nephropathy is a clinical diagnosis based on the finding of proteinuria in a patient with diabetes and in whom there is no evidence of urinary tract infection. Overt nephropathy is characterized by protein excretion greater than 0.5 g/day. This is equivalent to albumin excretion of around 300 mg/day. It is preferable to assess proteinuria as albuminuria because it is a more sensitive marker for CKD due to diabetes. The NKF-K/DOQI Work Group concluded that urinary albumin should be measured to detect and monitor kidney damage in adults. Patients are considered to have micro-albuminuria when the urinary albumin excretion is between 30 and 300 mg/day ***(Zerbini et al., 2006).***

In patients with type 1 diabetes, the microalbuminuria will progress to overt nephropathy at an average rate of 20% of non-diabetics over 5 years ***(Rigalleau et al., 2008).***Since the onset of type 2 diabetes is difficult to define, it is difficult to estimate the incidence of microalbuminuria. As albuminuria worsens and blood pressure increases, there is relentless decline in GFR. In some patients with microalbuminuria, renal lesions are already quite advanced and therefore, it may be a marker of nephropathy rather than a predictor of renal structural changes ***(Zerbini et al., 2006).***

There may be a genetic predisposition to develop diabetic nephropathy. Genetic determinants and their impact on the initiation and progression of diabetic nephropathy continue to be actively investigated. Numerous metabolic pathways and associated groups of genes have been proposed as candidates to play a role in the genetic susceptibility to nephropathy ***(Murphy et al., 2008).***

***2-*** **Hypertension/Ischemic Kidney Disease:**

Hypertension is the second most common attributed etiology of CKD in the world. There is abundant evidence that hypertension, especially systolic hypertension, is a powerful promoter of kidney damage. It may exacerbate the renal injury and rate of decline that occurs from a given disease ***(Hausberget al., 2008).***

The relationship between hypertension and CKD is difficult to establish because hypertension is a frequent consequence of CKD and thus is likely to be present in a large proportion of subjects with CKD regardless of their initial etiology ***(Padwal et al., 2008).*** However, there is also clear evidence that hypertension predates an increased risk of end-stage renal disease (ESRD). In addition, control of blood pressure clearly decreases the risk of CKD progression ***(Raoet al., 2008).***

Renal artery stenosis is one of the important causes of renal vascular hypertension; it causes flbromuscular hyperplasia which commonly occurs in women under the age of 50. The

remainder of renal vascular disease is due to atherosclerotic stenosis of the proximal renal arteries ***(Lee et al., 2006).****The* mechanism of hypertension is excessive renin release due to reduction in renal blood flow and perfusion pressure. Renal vascular hypertension may occur when a single branch of the renal artery is stenotic, but in as many as 25% of patients both arteries are obstructed ***(Hausberget al., 2008).***

**3- Post-Infectious Glomerulonephritis:**

Post-infectious glomerulonephritis is often associated with post-streptococcal infections due to nephritogenic group A beta-hemolytic Streptococci, especially type 2. It commonly appears after pharyngitis within one week after infection. Other causes of post-infectious glomerulonephritis include bacteremic states such as systemic Staphylococcus aureus infection, infective endocarditis and shunt infections ***(Blyth et al., 2007).***

Patients with post-infectious glomerulo-nephritis complain of oliguria, generalized edema and variable hypertension. Serum complement levels are low; antistreptolysin O titres (ASOT) can be high unless the immune response had been blunted with previous antibiotic treatment. Classically, the urine is described as cola-colored. Urinary red blood cells, red cell casts, and proteinuria under 3.5 g/day is present. Immunofluorescence shows IgG and C3 in granular basement membrane. Electron microscopy shows large, dense sub-epithelial deposits ***(Srisawatet al., 2006).***

**4- Berger's Disease (IgA Nephropathy):**

Berger's disease (IgA nephropathy) is a primary renal disease of IgA deposition in the glomerular mesangium. The inciting cause is unknown, but the same lesion is seen in Henoch-Schonlein purpura. IgA nephropathy is also associated with hepatic cirrhosis, celiac disease, and infections such as epithelial portion of glomerular capillary walls. The antigens in primary disease are not known. Secondary disease is associated with infections such as hepatitis B, endocarditis, and syphilis; autoimmune disease such as systemic lupus erythematosus, mixed connective tissue disease, and thyroiditis; carcinoma and certain drugs such as gold, penicillamine, and captopril. Membranous nephropathy occurs most commonly in adults at their fifth and sixth decades, and almost always after the age of 30 years ***(Lee et al., 2006).***

**5. Focal segmental glomerular sclerosis:**

This lesion can present as idiopathic disease or secondary to conditions such as heroin use, obesity, and HIV infection. Clinically, patients show evidence of nephrotic syndrome, but they also have more nephritic features than membranous nephropathy or minimal-change disease.

Eighty percent of patients have microscopic hematuria at presentation, and many are hypertensive. Decreased renal function is present in 25-50% of cases at time of diagnosis. The diagnosis requires renal biopsy. Light microscopy shows the lesions of focal segmental glomerular sclerosis. It is thought

that these lesions occur first in the juxta- medullary glomeruli and are then seen in the superficial renal cortex. IgM and C3 are seen in the sclerotic lesions on immunofluorescence. Electron microscopy shows fusion of epithelial foot processes as seen in minimal-change disease. Patients with focal segmental glomerular sclerosis and nephritic syndrome typically progress to end-stage renal disease in 6-8 years ***(Meyrier, 2005).***

**D. Stages of Chronic Kidney Disease:**

Chronic kidney disease is defined according to the presence or absence of kidney damage and level of kidney function irrespective of the type of kidney disease (diagnosis). Among individuals with chronic kidney disease, the stages are defined based on the level of kidney function. Staging of chronic kidney disease will facilitate application of clinical practice guidelines, clinical performance measures and quality improvement efforts to the evaluation, and management of chronic kidney disease ***(National Kidney Foundation K/DOQI, 2002).***

As a rule, kidney failure due to chronic kidney disease is preceded by a stage of variable length during which GFR is decreased. GFR is affected by a number of factors in addition to kidney disease, and not all individuals with decreased GFR have chronic kidney disease. Mild reduction in GFR is defined as chronic kidney disease only in the presence of kidney damage (Stage 2). However, because of the risk of complications, moderate (Stage 3) to severe (Stage 4) reduction in GFR and kidney failure (Stage 5) are defined as chronic

kidney disease, irrespective of the presence of kidney damage. Other than kidney disease, the most important factor affecting GFR is age. GFR rises during infancy and declines during aging. Therefore, mild reduction in GFR may be "normal" at the extremes of age and, in the absence of kidney damage, is not considered to be chronic kidney disease ***(National Kidney Foundation K/DOQI, 2002).*** Stages of chronic kidney disease as defined in the K/DOQI guidelines are seen in Table (1).

**Table (1):** Stages of Chronic Kidney Disease

| Stage | Description | GFR (mL/min/1.73m$^2$) | Action |
|---|---|---|---|
| | At increased risk | ≥ 90 (with CKD risk factors) | Screening CKD risk reduction |
| 1. | Kidney damage with normal or ↑ GFR | ≥90 | Diagnosis and treatment of co-morbid conditions, slowing progression, CVD risk reduction |
| 2. | Kidney damage with mild ± GFR | 60-89 | Estimating progression |
| 3. | Moderate ↓GFR | 30-59 | Evaluating and treating complications |
| 4. | Severe ↓ GFR | 15-29 | Preparation for kidney replacement therapy |
| 5. | Kidney Failure | <15 (or dialysis) | Replacement (if uremia is present) |

***(National Kidney Foundation K/DOQI, 2002).***

## E. Clinical Features of Chronic Kidney Disease:

Chronic kidney disease has been noted to lead to disturbances in function of every organ system.

### 1- General Features:

Patients with chronic kidney disease usually suffer from fatigue, malaise, and anorexia. Anemia is a major contributing factor to fatigability. Meanwhile, the malaise and anorexia are due to an effect of uremic toxins on the brain. In children, small

stature and growth failure are a major problem, particularly if chronic acidosis or renal bone disease are present ***(Muneer et al., 2004).***

**2- Fluid and Electrolyte Disturbances:**

Patients with renal failure have impaired renal mechanisms for adjusting body water. So, they are liable to volume overload or volume depletion, in response to excessive intake or excessive loss, respectively. In advanced CKD, the serum potassium concentration tends to be higher than normal. Hyperkalemia may be accentuated by trauma, surgery, anesthesia, blood transfusion, acidosis, or increased dietary intake. Many patients may remain asymptomatic until cardiac arrest occurs. The major warning signs are the electro-cardiography changes (widening of QRS complex and tall T-wave). The disordered renal mechanisms for sodium excretion, in their own, or the fluid imbalance make CKD patients liable for either hypernatremia or hyponatremia ***(Kraut, 2000).***

In CKD patients, hypocalcemia results from inability of the diseased kidney to activate vitamin D (1 α-hydroxylation step). This leads to impaired calcium absorption from the gut. Phosphate concentration begins to rise when GFR falls below 25 percent of normal. These changes stimulate parathyroid hormone secretion, which finally mobilizes calcium salts from bone leading to renal and metabolic osteodystrophy. Hyperuricemia and hypermagnesemia may be a common consequence of renal failure ***(Kates et al., 1997).***