INTRODUCTION

Despite improvements in dialysis treatment, patients on maintenance hemodialysis (HD) have a markedly higher mortality rate compared with the general population. According to the 2012 US Renal Data System (USRDS) report, the expected lifespan is 8 years for incident HD patients aged 40–44 years and 4.5 years for those aged 60–64 years (***Asci et al., 2016).***

The annual mortality from cardiovascular disease in end-stage renal disease (ESRD) is substantially higher than in the general population. Cardiovascular disease is the leading cause of morbidity and mortality in patient with ESRD, accounting for more than 50% of all deaths. Although classical coronary risk factors, such as hypertension and diabetes mellitus, are highly prevalent in patients with ESRD and are associated with poor cardiovascular outcome, such traditional risk factors do not fully account for the burden of cardiovascular disease in patients with ESRD ***(Negishi et al., 2010).***

Patients with end-stage renal disease are exposed to extreme volume shifts and thereby cardiovascular strain as a consequence of interdialytic weight gain, fluid removal during hemodialysis and also chronic fluid overload ***(Antlanger et al., 2013).***

Fluid overload in hemodialysis patients sometimes requires emergent dialysis, Managing fluid status of dialysis patients remains a challenge. Because dialysis patients are usually oliguric or anuric, their tendency to accumulate fluid must be managed through a combination of limiting salt and fluid intake and ultrafiltration during dialysis sessions***(Arneson et al., 2010)***.

Patients are associated with adverse outcomes including hypertension, exacerbation of congestive heart failure (CHF), and increased risk of death ***(Arneson et al., 2010).***

In long-term hemodialysis patients, higher IDWG (interdialytic weight gain) is associated with poor survival and increased cardiovascular death. Patients with the lowest interdialytic fluid retention have the greatest survival ***(Kalantar-Zadeh., 2009).***

Patients with IDWG ≥ 5.7% of dry weight, one of the criteria used to define non-compliance, were also found to have a higher mortality risk. Moreover, ***Kalantar-Zadeh et al. (2009).*** Revealed that the risks of all-cause and cardiovascular mortality were significantly higher in long-term HD patients with IDWG ≥ 4.0 kg. Furthermore, a very recent study demonstrated that IDWG >3.0 kg was associated with a 1.29-fold increase in all-cause mortality, independent of dialysis session length ***(Lee et al., 2014).***

LVH is a cardiovascular complication among renal patients. Pathophysiologic factors involved in LVH of CKD and ESRD patients have generally been divided into three categories: (1) related to afterload, (2) related to preload, and (3) not related to afterload or preload. The ones in the first category are represented by an increase in systemic arterial resistance, elevated arterial blood pressure, and reduced large-vessel compliance related in part to aortic 'calcification', which is typical in CKD patients; all these factors result in myocardial cell thickening and concentric LV remodeling often together with activation of the intracardiac renin-angiotensin system ***(Lullo et al., 2015).***

Oxidative stress and xanthine oxidase activation as well as the phosphodiesterase-5 pathway may also be involved in the development of LVH as demonstrated by pharmacological effects of sildenafil therapy that attenuates LVH. Among the preload-related factors, the role of intravascular volume expansion (salt and fluid loading) has to be underlined, as well as secondary anemia and the presence of arterovenous fistulas, resulting in myocardial cell lengthening and eccentric or asymmetric LV remodeling. Both afterload- and preload-related factors operate with additive and synergistic effects ***(Lullo et al., 2015)***.

Fibroblast growth factor-23 (FGF-23) is an osteocyte-derived phosphaturic hormone which, in combination with its cofactor, Klotho, inhibits production of 1, $25(OH)_2$ vitamin D

by reducing the activity of renal 1α-hydroxylase. In patients with chronic kidney disease, FGF-23 levels rise in response to a combination of factors, including decreasing filtration and/or degradation by the diseased kidney, phosphate retention and Klotho deficiency ***(Venrooij et al., 2014).***

Genetic and biochemical evidence indicates that FGF-23 reduces the serum phosphate concentration. The serum concentration of FGF-23 increases as kidney function declines, and its levels are extremely high in hemodialysis patients, although the role of FGF-23 in patients without kidney disease is generally unknown ***(Negishi et al., 2010)***.

In addition to its endocrine actions at the level of the kidney, several recent epidemiologic studies suggest that elevated circulating levels of FGF-23 may be an independent risk factor for cardiac disease and early mortality in patients with all stages of CKD ***(Venrooij et al., 2014).***

It was found that increased interdialytic volume load is associated with increased both LVMI and FGF-23 level ***(Unver et al., 2015)***.

Chapter 1

CARDIOVASCULAR DISEASES IN HEMODIALYSIS PATIENTS

Chronic kidney disease is an important cause of global morbidity and mortality. In the 2013 Global Burden of Disease study, 956 200 people were estimated to have died from chronic kidney disease, a 134% increase from 1990, one of the largest rises among the top causes of death. Furthermore, even in the early stages of chronic kidney disease, the risk of fatal and non-fatal cardiovascular events attributable directly to renal disease rises substantially ***(Ene-lordache et al., 2016).***

Thus, kidney disease should be a global public health priority, particularly because, worldwide, more than 1.4 million individuals with end-stage renal disease are estimated to receive renal replacement therapy with dialysis or transplantation, with 8% annual growth (***Ene-lordache et al., 2016)*.**

Creatinine is a poor indicator of renal function, and glomerular filtration rate (GFR) estimation is preferred in the assessment of renal function. GFR is an independent prognostic marker in various heart failure (HF) populations ***(O'Meara et al., 2006).***

A GFR below 60 ml/min/1.73m2is associated with complications of renal disease. In patients with end-stage HF, irreversibly impaired renal function precludes eligibility for

heart transplantation, and a simple method to accurately estimate renal function is of paramount importance. Although the Modification of Diet in Renal Disease (MDRD) equations have been used to estimate GFR in HF studies, these have not been validated in patients with severe co-morbid conditions, including HF ***(O'Meara et al., 2006).***

The incidence of chronic kidney disease is at least 3-4 times more frequent in Africa than in developed countries but the prevalence of ESRD is relatively lower which reflects lack of medical care facilities ***(El Minshawy, 2011).***

In Egypt, the prevalence of dialysis patients is presumed to be increasing and the main causes of ESRD in Egypt, other than diabetic nephro-pathy, included hypertensive kidney disease, chronic glomerulonephritis, unknown etiology, chronic pyelonephritis, schistosomal obstrctive uropathy and schistosomal nephropathy ***(El Minshawy, 2011).***

WHO statistics for Egypt as of 2009 showed that: Infectious diseases are still a major health problem in Egypt. Cardiovascular diseases have significantly increased in the last two decades. ESRD has shown an almost exponential growth. Major sociodemographic changes have occurred in Egypt to promote the development of noncommunicable diseases ***(Soliman et al., 2012).***

A) Risk factors of CKD:

Major risk factors for CKD progression after AKI include advanced age, diabetes mellitus, hypertension, heart failure, increased Charlson co-morbidity score during AKI episode, preexisting CKD (as defined by proteinuria or reduced GFR), and low levels of serum albumin, a dual marker of nutrition and inflammation ***(Goldstein et al., 2013).***

B) Causes of ESRD:

Chronic kidney disease is a worldwide public health problem with increasing prevalence and incidence, high cost and adverse outcomes such as vascular disease and premature death. Advanced stages of CKD mean death over a short time period in most cases ***(Jayasumana et al., 2017).***

Well-known causative factors of CKD include mainly diabetes, hypertension and well-characterized renal syndromes. In addition to these 'traditional' causes, glomerular and tubulo-interstitial diseases due to infections, nephrotoxic drugs, herbal medications, and environmental and occupational exposure to toxicants contribute substantially to CKD, particulary in low and mid income countries (LMIC), ***(Jayasumana et al., 2017).***

In el Minia governorate in Egypt; Diabetes mellitus was the leading cause of ESRD in patients who underwent hemodialysis (34.7%), followed by hypertension (21.5%) and obstructive uropathy (11.3%). These features are similar to

those reported by other countries in the developed world ***(Soliman et al., 2012).***

The number of patients developing End stage renal disease as a consequence of hypertension is increasing in Egypt. It is also proposed that mild to moderate hypertension can lead to ESRD. Early investigators note that nephrosclerosis was correlated with hypertension and/or left ventricular hypertrophy ***(Soliman et al., 2012).***

In many Arab countries, obstructive uropathy constitutes a major cause of ESRD (40%). The two most common underlying causes are renal calculi and schistosomiasis. In many developing countries, chronic glomerulonephritis is often caused by infections and infestations, and is a leading cause of CKD. Tobacco use is positively associated with CKD. Alcohol has been linked as a cause of kidney disorders in some clinical and experimental studies. Also obesity seems to be an important and preventable risk factor for chronic renal failure ***(Ghonemy et al., 2016).***

C) Pathology and pathogenesis:

a- Pathogenesis of CKD:

The pathogenesis of chronic kidney disease is very different from that of acute kidney disease. Acute injury of the kidney results in death and sloughing of tubular epithelial cells most probably followed by there regeneration with

reestablishment of normal architechere. Chronic injury results in irreversible loss of nephrons ***(Block et al., 2004).***

As a result, a greater functional burden is born by fewer nephrons manifested as an increase in glomerular filtration pressure and hyperfiltration. This compensatory hyperfiltration which can be thought as a form of hypertension at the level of the individual nephron predispose to fibrosis and scarring which is call glomerulosclerosis. So the rate of nephron destruction and loss increases progression to uremia ***(Go et al., 2004).***

b- Pathogenesis of uremia:

The pathogenesis of CKD is in part from a combination of the toxic effect of retained waste product normally excreted by the kidneys (nitrogen containing products of protein metabolism), normal products such as hormones now present in increased amounts or loss of normal products of the kidney (loss of erythropoietin) ***(Szczech., 2004).***

Excretory failure results also in fluid shift with increased intracellular Na and water with decreased intracellular K, this alterations may contribute to alterations in function of a host of enzymes transport system and so on ***(Go et al., 2004).***

Finally, uremia has a number of effects on metabolism that are currently not well understood including a decrease in

basal body temperature and diminished lipoprotein lipase activity with accelerated atherosclerosis ***(Block et al., 2004).***

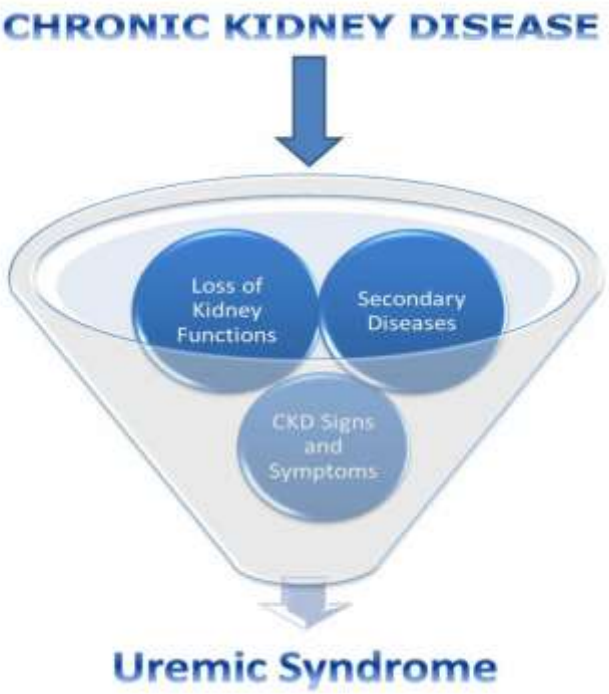

Figure (1): Uremic syndrome.

Although the great improvements in dialysis treatment, patients on regular haemodialysis have a higher mortality rate in comparison with the general population. There are significant inter-country differences in annual mortality rates of HD patients. This disparity may partially be explained by the differences in mortality rates of the general population in the various countries. Additionally, variations in patient age, prevalence of comorbid diseases, underlying renal disease and racial/genetic status all contribute to survival of dialysis patients. Finally, differences in practice patterns also impact

survival rates, e.g. weekly dialysis duration, vascular access type, physician care and management of hypertension, hyperphosphataemia and anaemia ***(Asci et al., 2016).***

Patients with end-stage renal disease are exposed to extreme volume shifts and thereby cardiovascular strain as a consequence of interdialytic weight gain, fluid removal during hemodialysis and also chronic fluid overload. Fluid overload leads to distorted hemodynamic conditions, and most probably higher cardiovascular morbidity. Several biomarkers of cardiovascular risk have been studied in hemodialysis patients during the recent years, yet their clinical significance remains vague ***(Antlanger et al., 2013)***.

Fluid retention is a major clinical problem in individuals with advanced chronic kidney disease (CKD), also known as stage 5 CKD or end-stage renal disease, and is associated with morbid conditions such as lower-extremity edema, anasarca, ascites, pulmonary vascular congestion or edema, hypertension, and worsening heart failure ***(Kalantar-Zadeh et al., 2009).***

Not infrequently, dialysis treatment needs to be initiated to prevent or treat complications related to fluid retention, especially when diuretic therapy fails. Hence, removal of fluid during the dialysis treatment, also known as ultrafiltration, is the cornerstone of volume management in advanced stage CKD ***(Kalantar-Zadeh et al., 2009).***

Ultrafiltration is also used occasionally in heart failure patients resistant to medical treatment. A main challenge related to ultrafiltration interventions is assessment of the required magnitude and frequency of fluid removal; however, it is not clear whether fluid removal can improve clinical outcomes in CKD or heart failure patients ***(Kalantar-Zadeh et al., 2009).***

Further research regarding the association between biomarkers for cardiovascular disease and fluid overload is warranted. Chronic subclinical inflammation may be an additional contributing factor in the linked processes of repeated fluid removal and cardiac stress. It has been suggested that hemodialysis patients are exposed to high endotoxin levels in the blood, possibly due to repeated bacterial translocation from the gut as a consequence of intradialytic changes in blood pressure and/ or tissue perfusion ***(Antlanger et al., 2013).***

Fluid overload has recently been shown to result in adverse outcomes for hemodialysis patients. For many years, a normohydrated fluid status has been regarded an issue of vital importance to reduce deranged fluid homeostasis and cardiac morbidity and mortality ***(Antlanger et al., 2013).***

One of the greatest challenges for physicians caring for hemodialysis (HD) patients is assessing their extra-cellular fluid volume ***(Ishibe et al., 2004).***

While the physical examination is a classic tool for the evaluation of volume status, there are several problems related to its use. There has been a progressive loss of interest for practicing physicians in bedside diagnosis, coupled to a decline in the clinical performance of students and training physicians, and the often lacking evidence-based analysis of specific physical findings. In the particular case of volume assessment, available evidence suggests that the examination lacks sensitivity and specificity in the diagnosis of either hypovolemia or volume overload ***(Ishibe et al., 2004).***

The assessment of inferior vena cava (IVC) diameter and its collapse with inspiration have been the most commonly used echocardiographic techniques to assess intravascular volume. However, two other echocardiographic methods, hepatic vein Doppler to assess right atrial pressure and the left atrial diameter, have not been assessed ***(Agarwal et al., 2011).***

Much attention has been given to biochemical markers of changes in extracellular volume. A large body of literature can be found on the use of atrial natriuretic peptide (ANP) and its second messenger cyclic GMP (cGMP) to identify patients with increased plasma volume in renal failure ***(Ishibe et al., 2004).***

Natriuretic peptides play a major role in salt and water homeostasis, protecting the cardiovascular system from the effects of volume overload. ANP (28 amino acids) and BNP

(32 amino acids) share a common 17-aminoacid ring structure. Both peptides are released primarily from the heart and act in various tissues inducing vasodilatation, natriuresis and dieresis ***(Sivalingam et al., 2015).***

Atrial naturetic peptide (ANP) is predominantly synthesised in the atria also synthesised in either chamber under pathological conditions. ANP is stored in atrial granules and released even with minor increases in volume ***(Sivalingam et al., 2015).***

Brain natriuretic peptide (BNP) is secreted by cardiomyocytes under stretch condition. In heart failure patients, high BNP blood levels are associated with decreased patient survival. This association has also been reported in hemodialysis patients, for whom it is difficult to know whether a BNP increase is related to the cardiac condition, fluid excess, or both ***(Chazot et al., 2015).***

It was found that BNP is a strong predictor of both left ventricular mass and ejection fraction. However, we found in a small cohort of incident HD patients that the initial fluid removal is significantly associated with BNP decrease. It is suggested that BNP is a surrogate of fluid excess and its consequences on the cardiac structure ***(Chazot et al., 2015).***

Both ANP and BNP have been investigated as markers of hydration in dialysis patients. Mean ANP levels are

markedly increased in dialysis patients, decrease with ultrafiltration but remain constant during isovolaemic HD suggesting that reduced synthesis in response to decreasing circulating volume is their main determinant ***(Sivalingam et al., 2015).***

Elevated ANP levels post-dialysis are associated with fluid overload. Consistent weight reduction was followed by a decrease of ANP levels but the levels remained high compared with levels normal subjects. Blood levels of BNP also reflect volume status in dialysis patients. In addition they are strongly associated with left ventricular dysfunction ***(Sivalingam et al., 2015).***

To date, only serum N-terminal brain natriuretic peptide (BNP) levels are known to be strongly associated with fluid overload and have recently even been suggested as a guide for fluid management in hemodialysis patients. Troponin T (TnT) and D-Dimer have been shown to be elevated in the dialysis population in general, but a direct association with fluid overload has not been demonstrated for TnT, or has not yet been studied, as in the case of D-dimer ***(Antlanger et al., 2013).***

In hemodialysis patients, high interdialytic weight gain, high ultrafiltration rate, and short session duration have been associated with poor outcomes. Specifically, high IDWG, as defined by various cutoffs, has been associated with increased