EVALUATION OF CHRONIC KIDNEY DISEASE AND MEDICATION PRESCRIBING PATTERNS IN A SINGLE TERTIARY CARE CENTER IN MALAYSIA

by

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DEDICATION

It is with my deepest gratitude and warmest affection that I dedicate this thesis to my parents

Prof. Dr. Khalid Hussain and Fehmida Kausar

for being a constant source of knowledge and inspiration

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All praise to Almighty Allah, the Lord of this world and hereafter, the absolute source knowledge of every type, and Prophet Muhammad (peace be upon him), a beacon of knowledge for the mankind. Nothing can happen without the will/wish of Allah (SWT).

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LIST OF ABBREVIATIONS

ACR	Albumin –to-creatinine ratio
AER	Albumin excretion rate
AST	Aspartate transaminase
APKD	Adult polycystic kidney disease
ADR	Adverse drug reactions
ACEIs	Angiotensin converting enzyme inhibitors
ALP	Alkaline phosphatase
ARBs	Angiotensin receptor blockers
ATC	Anatomical Therapeutic Classification
BP	Blood Pressure
BMI	Body mass index
CG	Cockcroft-Gault
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology
Ccr	Creatinine clearence
CVD	Cardiovascular disease
CAPD	Continuous ambulatory peritoneal dialysis
CKD-MBD	Chronic kidney disease-mineral bone disorders
CGN	Chronic glomerulonephritis
CRF	Chronic renal failure
CPN	Chronic pyelonephritis
CCB	Calcium channel blockers
Ca-P	Calcium-phosphorus product
CCF	Congestive cardiac failure

DM	Diabetes mellitus
DN	Diabetic nephropathy
ESRD	End-stage renal disease
ESRF	End-stage renal failure
EPO	Erythropoietin
GFR	Glomerular filtration rate
GN	Glomerulonephritis
HPT	Hypertension
HPL	Hyperlipidemia
HD	Hemodialysis
HDL	High density lipoprotein
Hb	Hemoglobin
HCT	Hematocrit
HUSM	Hospital Universiti Sains Malaysia
IWD	Indication without drug therapy
IHD	Ischemic heart disease
KDIGO	Kidney Disease: Improving Global Outcomes
KEEP	Kidney Early Evaluation Program
KUB	Kidney, ureter and bladder
K-DOQI	Kidney disease Outcomes Quality Initiative
LDH	lactate dehydrogenase
LDL	Low density lipoprotein
MDRD	Modification of Diet in Renal Disease
MDTR	Malaysian Dialysis and Transplant Registry
MI	Myocardial infarction

MRPs	Medication related problems
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
NSAIDs	Non-steroidal anti-inflammatory drugs
OBS	Obstructive uropathy
PMP	Per million populations
PD	Peritoneal dialysis
PCA	principal component analysis
PBs	Phosphate binders
PVD	Peripheral vascular disease
RAAS	Renin-angiotensin-aldosterone system
RRT	Renal replacement therapy
RBCs	Red blood cells
SLE	Systemic lupus erythematosus
SPSS	Statistical Package for the Social Sciences
Scr	Serum creatinine
SCys C	Serum cystatin C
TN	Toxic nephropathy
US	United States
USRDS	United States Renal Data System

PENILAIAN BERKENAAN PENYAKIT BUAH PINGGANG KRONIK DAN CORAK PRESKRIPSI UBAT-UBATAN DI SEBUAH PUSAT RAWATAN TERTIARI DI MALAYSIA

ABSTRAK

Penyakit buah pinggang kronik merupakan masalah perubatan sejagat yang semakin meningkat, ia menjejaskan sosioekonomi keluarga pesakit dan juga negara, maklumat berkenaan punca penyakit tersebut dan corak preskripsi ubat-ubatan yang diperlukan untuk memperbaiki hasil klinikal jarang didapati di Malaysia. Oleh yang demikian kajian ini bertujuan untuk menilai punca-punca penyakit buah pinggang kronik dan ubat-uabatn yang digunakan oleh rakyat Malaysian yang mengalami penyakit buah pinggang kronik. Kajian retrospektif, keratan rentas ini telah dilaksanakan ke atas pesakit dewasa yang mengalami penyakit buah pinggang kronik, yang mendapat rawatan di Hospital Universiti Sains Malaysia, daripada 1 Januari 2009 hingga ke 31 Disember 2013. Data pesakit berkenaan dengan sosiodemografik, laporan makmal, punca-punca penyakit, peringkat penyakit buah pinggang kronik dan jenis ubat-ubatan telah dikumpulkan. Ubat-ubatan tersebut telah diklasifikasikan berdasarkan "Anatomical Therapeutic Chemical Classification" seperti yang telah dicadangkan oleh Pertubuhan Kesihatan Sedunia. Perbandingan telah dilakukan di anatara kumpulan umur (bawah 50 tahun atau lebih 50 tahun), jantina, status diabetik dan peringkat penyakit buah pinggang kronik. Sejumlah 851 pesakit telah dimasukkan dengan nisbah antara lelaki ke perempuan pada 1.75:1.00 dengan purata umur 61.18 ± 13.37 tahun. Penyakit buah pinggang kronik peringkat 5 meliputi seramai 333 (39.1%) kes, manakala peringkat 4, 3b, 3a dan 2 kes adalah sebanyak 240 (28.2%), 186 (21.9%), 74 (.8.7%) dan 18 (2.1%) masing-masing. Berdasarkan sampel populasi, diabetic nefropati (DN) (44.9%) merupakan punca utama penyakit buah pinggang kronik, diikuti hipertensi (24.2%) dan obstruktif uropati (9.2%). Punca yang tidak

diketahui meliputi 9.4% daripada kes-kes. Perbezaan diantara insiden penyakit buah pinggang kronik disebabkan oleh diabetik nepfropati, hipertensi, glomerulonefritis, pesakit yang berumur di bawah 50 tahun dan pesakit melebihi 50 tahun mempunyai nilai statistik yang signifikan ($p = 0.008$, $p<0.001$ dan $p < 0.001$, masing-masing). Pesakit-pesakit telah diberikan pelbagai jenis preskripsi iaitu 12.10 ± 4.68 jenis ubat-ubatan. Lima kumpulan ubat-ubatan teratas adalah ubat-ubatan anti-lipid, "calcium channel blockers", "antiplatelet", "diuretik" dan ubat-ubatan untuk masalah ketidakseimbanagn asid. Penggunaan suboptimal beberapa kumpulan ubat-ubatan adalah agak ketara. Umur pesakit dan jantina tidak mempengaruhi jumlah ubat-ubatan yang digunakan ($p = 0.09$ dan $p = 0.40$ masing-masing). Pesakit diabetes telah diberikan preskripsi ubat-ubatan yang lebih berbanding pesakit lain (13.96 ± 4.78 vs 10.71 ± 3.60 $p = 0.001$). Tambahan lagi, jumlah preskripsi ubat-ubatan meningkat secara sangat signifikan dengan penurunan fungsi buah pinggang mengikut turutan (penyakit buah pinggang peringkat 2 dan 3a < peringkat 3b< peringkat 4 < peringkat 5 predialisis < peringkat 5 sedang menjalani dialysis). Keputusan kajian ini menunjukkan diabetik nefropati merupakan punca utama penyakit buah pinggang kronik diikuti oleh penyakit darah tinggi. Kajian ini juga turut menunjukkan penggunaan ubat-ubatan dalam kalangan pesakit buah pinggang kronik di Malaysia. Penggunaan sesetengah kumpulan ubatan secara suboptimal agak ketara dan usaha yang instruktif ke arah ini akan memberikan hasil yang lebih baik.

EVALUATION OF CHRONIC KIDNEY DISEASE AND MEDICATION PRESCRIBING PATTERNS IN A SINGLE TERTIARY CARE CENTER IN MALAYSIA

ABSTRACT

Chronic kidney disease (CKD) is an escalating medical problem worldwide, effecting socioeconomic conditions of patient's family and country, and information about its etiologies and medication prescribing patterns, needed to improve a better clinical outcome, is sparse in Malaysia. Therefore, this study is intended to evaluate the etiologies of CKD and medication use in Malaysian patients suffering from CKD. A retrospective, cross-sectional study was conducted on adult CKD patients, receiving treatment at Hospital Universiti Sains Malaysia, Kelantan, Malaysia from 1st January 2009 to 31st December 2013. Data regarding patient socio-demographics, laboratory investigations, etiology, stage of CKD and medications were collected. Individual drugs were classified according to the Anatomical Therapeutic Chemical Classification as recommended by the World Health Organization (WHO). Comparison was made between age groups (≤ 50 or > 50 years), gender, diabetic status and CKD stages. A total of 851 eligible cases were included with male to female ratio of 1.75: 1.00 and mean age of 61.18 ± 13.37 years. CKD stage 5 was accounted in 333 (39.1%) cases whereas stage 4, 3b, 3a and 2 cases were 240 (28.2%), 186 (21.9%), 74 (8.7%) and 18 (2.1%), respectively. In the sample population, diabetic nephropathy (DN) (44.9%) was found to be the foremost etiology of CKD, followed by hypertension (HPT) (24.2%) and obstructive uropathy (OBS) (9.2%). Unknown etiology constituted 9.4% of our cases. The difference of incidence of CKD due to DN, HPT, GN, patients of age ≤ 50 years and patients of age > 50 years was statistically significant ($P = 0.008$, $P < 0.001$ and $P < 0.001$, respectively). Patients were prescribed 12.10 ± 4.68 medications. The top five prescribed

medication groups were found to be lipid lowering agents, calcium channel blockers, antiplatelet agents, diuretics and drugs for acid related disorders. Underutilization of several classes of medications was apparent. Patient age and gender did not influence the number of medications used (P = 0.09 and P = 0.40, respectively). Diabetic patients were prescribed more drugs than patients without DM (13.96 ± 4.78 vs 10.71 ± 3.60 p = 0.001). Moreover, the number of prescribed medications significantly increased with declining renal function with a hierarchy (stage 2 and 3a < stage 3b < stage 4 < stage 5ND < stage 5D). The results of the present study indicate that diabetic nephropathy is the chief cause of CKD followed by hypertension. This study also provides an overview of medication use in a Malaysian CKD population. Underutilization of some medication classes is apparent and instructive efforts in this direction may ascertain better outcomes.

CHAPTER 1

INTRODUCTION

1.1 General Introduction

Kidney disease can either be acute or chronic. Acute kidney injury is the reversible decline in kidney function whereas chronic kidney disease (CKD) or chronic renal disease is the progressive destruction of kidney mass through loss of nephrons and irreversible sclerosis over a period of months or years (Gooneratne et al., 2008).

CKD is a major health problem across the globe (Levey et al., 2009) and attention paid towards CKD is attributable to five factors; escalating prevalence, enormous treatment cost, recent data tell-tale that overt disease (stage 3 to 5) is merely the tip of an iceberg of furtive disease (stage 1 to 2), its major involvement in increasing risk of cardiovascular events and discovery of effective measures to retard its progression (Barsoum, 2006).

1.2 Definition and classification of chronic kidney disease

1.2.1 Definition and criteria for chronic kidney disease

CKD is defined by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (2013) as "abnormalities in kidney structure or function, present for more than three months". The diagnostic criteria for CKD are shown in Table 1.1.

Table 1.1: Criteria for chronic kidney disease (Presence of either of the following for > 3 months)

Declined glomerular filtration rate	GFR < 60 ml/min/1.73m^2
Indicators of kidney damage	• Albuminuria (albumin excretion rate ≥ 30 mg/24hours; albumin-to-creatinine ratio ≥30/g) • Urine sediment (casts and tubular epithelial cells) anomalies • Electrolytes or other abnormalities due to tubular disorders • Structured deformities identified by renal imaging • Kidney transplantation history

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013); GFR-glomerular filtration rate

1.2.2 Classification of chronic kidney disease

As per KDIGO guidelines (2013), CKD should be classified according to etiology, glomerular filtration rate (GFR) and albuminuria. Etiology of CKD is based on the presence or absence of systemic disease and the location inside the kidney of the observed or presumed pathological-anatomic findings. Normotensive young adults have GFR of approximately 120-130 ml/min/1.73m^2 body surface area and declines with the age (Stevens & Levey, 2004). Classification of CKD according to GFR is presented in Table 1.2.

Table 1.2: Stages of chronic kidney disease based on glomerular filtration rate

Stage of CKD	Description	GFR (ml/min/1.73m^2)
Stage 1	Kidney damage and normal or increased kidney function	$\geq$ 90 ml/min/1.73m^2
Stage 2	Kidney damage with mild decrease in kidney function	60-89 ml/min/1.73m^2
Stage 3a	Mild to moderate decrease in Kidney function	45-59 ml/min/1.73m^2
Stage 3b	Moderate to severe decline in Kidney function	30-44 ml/min/1.73m^2
Stage 4	Severe decline in kidney function	15-29 ml/min/1.73m^2
Stage 5	Kidney failure	< 15 ml/min/1.73m^2

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013); CKD-chronic kidney disease; GFR-glomerular filtration rate

As described in Table 1.2, renal function continually decline from Stage 1 to stage 5. In the early stages of CKD, kidneys are able to adapt to the injury and maintain the GFR by increasing intraglomerular pressure and filtration rate by the remaining nephrons called hyper-filtration. Due to this mechanism early stages of CKD are under-diagnosed. But in the long run, the increased intraglomerular pressure further damages the remaining nephrons leading to kidney failure manifested by proteinuria (Haynes & Winearls, 2010). The categories of albuminuria as per KDIGO criteria are shown Table 1.3.

Table 1.3: Albuminuria categories in chronic kidney disease

Category	Description	Albumin excretion rate	Albumin-to-creatinine ratio
A1	Normal to mild increase	< 30 mg/24 hours	< 30 mg/g
A2	Moderate increase	30-300 mg/24 hours	30-300 mg/g
A3	Severe increase	> 300 mg/24 hours	> 300 mg/g

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013)

1.3 Symptoms of chronic kidney disease

CKD is considered as a silent disease because its symptoms are subtle. The symptoms typically develop in late stages of CKD and usually only when end-stage renal disease (ESRD) is impending (Haynes & Winearls, 2010). The clinical manifestations including vomiting, anorexia, itching and muscle cramps –if attributable to CKD- are the indication of prompt initiation of renal replacement therapy (RRT) (Haynes & Winearls, 2010). Moreover, CKD patients also complain of dyspnea, edema and oliguria (Ulasi & Ijoma, 2010) The symptoms of CKD like vomiting and diarrhea further lead to nausea, dehydration and loss of weight because of increased level of urea in the body (Manley et al., 2012). Abnormal heart rhythm and muscle paralysis commonly experienced by CKD sufferers due to hyperkalemia (Einhorn et al., 2009). Proteinuria as a result of hyper-filtration is also a sign of CKD (Haynes & Winearls, 2010).

1.4 Estimation of renal function

The best index to measure renal function is GFR (Lascano & Poggio, 2010). GFR is the product of mean filtration rate of each sole nephron multiplied by the total number of nephrons present in both kidneys (Floege, Jhonson, & Feehally, 2010). Normal GFR level is around 130 ml/min/1.73m^2 for men and 120ml/min/1.73m^2 for women, with significant difference amongst individuals based on age, gender, body mass, diet, physical activity, pharmacological therapy, and physiological states e.g. pregnancy (Floege et al., 2010). The adult GFR can be computed by applying Cockcroft-Gault (CG) equation, Modification of Diet in Renal Disease (MDRD) study equation, Chronic kidney disease- Epidemiology (CKD-EPI) creatinine equation, CKD-EPI cystatin C equation and CKD-EPI creatinine-cystatin C equation.

1.4.1 Cockcroft-Gault (CG) equation

In 1973, CG equation was developed to predict the creatinine clearance (Ccr) from serum creatinine (Scr), age and body weight (Cockcroft & Gault, 1976). The CG formula is expressed below:

$$Ccr = (140 - age) \times weight\ (Kg) / 72 \times Scr\ [\times 0.85 \text{ if female}]$$

1.4.2 Modification of Diet in Renal Disease (MDRD) study equation

The MDRD study equation was developed in 1999 using data including Caucasian and African-American CKD patients with GFR from 5-90 ml/min/1.73m^2 body surface area as stated under:

$$\text{MDRD eGFR} = 186 \times (Scr)^{-1.154} \times (age)^{-0.023}\ [\times 0.742 \text{ if female}]\ [\times 1.21 \text{ if black}]$$

The aforementioned equation only requires data of serum creatinine, age and gender (Levey et al., 2000).

1.4.3 Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation

The MDRD study equation was developed in CKD population and its major limitations were imprecision and systematic underestimation of GFR at levels > 60ml/min/1.73m^2 (Stevens et al., 2007). Therefore, a more accurate equation named CKD-EPI creatinine equation was designed in 2009 (Levey et al., 2009). The CKD-EPI equation is given below:

$$eGFR = 141\times \min(S_{cr}/k, 1)^{\alpha} \times \max(S_{cr}/k, 1)^{-1.209} \times 0.993^{Age} [\times 1.018 \text{ if female}] [\times 1.159 \text{ if black}]$$

Where S_{cr} is Serum creatinine (mg/dl); k is 0.7 for females and 0.9 for males; α is -- 0.329 for females and -0.411 for males; min is minimum of S_{cr}/k or 1; max is maximum of S_{cr}/k or 1

In the comparative performance of MDRD formula and CKD-EPI creatinine formula, the latter formula was proven to be more accurate (Stevens et al., 2010). Maisarah et al. (2014) conducted a cross-sectional study to compare the performance of CKD-EPI and MDRD equations in multiethnic Malaysian population attending University Malaya Medical Centre. They reported that for eGFR < 30 ml/min/1.73m^2 and 30-59 ml/min/1.73m^2 both equations had similar bias (median difference compared with measured GFR) but for eGFR 60-89 ml/min/1.73m^2, bias decreased from 12.3

(MDRD equation) to 7.3 ml/min/1.73m^2 (CKD-EPI equation) (41% improvement). Furthermore, for eGFR > 90 ml/min/1.73m^2, bias was decreased from 11.7 (MDRD equation) to 11.5 ml/min/1.73m^2 (CKD-EPI equation). Therefore, they concluded that CKD-EPI equation was more accurate than MDRD equation in estimating GFR > 60 ml/min/1.73m^2.

1.4.4 CKD-EPI cystatin C equation

Serum cystatin C level alone -as a replacement for Scr in estimation of renal function- provided GFR estimates as accurate as Scr (Stevens et al., 2008). The CKD-EPI cystatin C equation is stated as:

$$eGFR = 133 \times \min(SCysC/0.8, 1)^{-0.499} \times \max(SCysC/0.8, 1)^{-1.328} \times 0.996^{Age} [\times 0.932 \text{ if female}]$$

Where SCysC is Serum cystatin C; min is minimum of SCysC/0.8 or 1; max is maximum of SCysC/0.8 or 1

1.4.5 CKD-EPI creatinine-cystatin C equation

The equation comprising SCys C level in combination with Scr level, sex, age and race provided the supreme accurate GFR estimates (Stevens et al., 2008). The CKD-EPI creatine-cystatin C equation is given below:

$$eGFR = 135 \times \min(Scr/k, 1)^{\alpha} \times \max(Scr/k, 1)^{-0.601} \times \min(SCysC/0.8, 1)^{-0.375} \times \max(SCysC/0.8, 1)^{-0.711} \times 0.995^{Age} [\times 0.969 \text{ if female}] [\times 1.08 \text{ if black}]$$

Whereby S_{cr} is Serum creatinine (mg/dl); SCysC is Serum cystatin C (mg/l); k is 0.7 for females and 0.9 for males; α is -0.248 for females and -0.207 for males; min(S_{cr}/k , 1) is minimum of S_{cr}/k or 1; max(S_{cr}/k, 1) is maximum of S_{cr}/k or 1; min(SCysC/0.8, 1) is minimum of SCysC/0.8 or 1; max(SCysC/0.8, 1) is maximum of SCysC/0.8 or 1

1.5 Assessment of individuals with higher risk for chronic kidney disease

The predictors of CKD are hypertension, diabetes mellitus, older age (≥ 60 years), urinary tract infections, systemic infections, auto-immune diseases, nephrotoxic agents, cardiovascular disease (CVD), kidney stone, kidney cysts, hyperlipidemia, smoking, obesity and higher consumption of alcohol (Levey et al., 2003; Yamagata et al., 2007). Individuals with aforesaid risk factors of CKD should be assessed and managed to impede the progression of kidney damage.

1.6 Assessment of proteinuria

Normal kidneys excrete a very minor amount of protein but a persistent higher level of albumin excretion or ACR ≥ 30mg/g is an indicator of kidney damage (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013). The kidney damage is linked with co-existing illnesses such as diabetes, hypertension and glomerular disease whereas the elevation in the excretion of low-molecular weight globulins is the indicator of tubolointerstitial disease (Levey et al., 2003).

1.7 Epidemiology of chronic kidney disease

1.7.1 Prevalence of chronic kidney disease

The prevalence of CKD varies from country to country. The median prevalence of CKD in individuals aged ≥ 30 years old was 7.2% whereas its prevalence in persons aged ≥ 64 years old ranged from 23.4-35.8% (Zhang & Rothenbacher, 2008). The prevalence of CKD was 15.6% and 8.5% in US and Mexico, respectively (Brown et al., 2003; Coresh et al., 2003). In another study from US, the estimated prevalence of CKD in non-institutionalized population was 4.5% (by MDRD equation) and 7.0% (by CG equation) (Coresh et al., 2005). In Canada, the estimated prevalence of CKD (participants from community-dwelling elderly in Calgary Health Region, aged ≥ 66 years) was 35.4% (Hemmelgarn et al., 2006).

The prevalence of CKD in European countries was 4.7% in Norway (Hallan et al., 2006), 6.4% in Italy (Cirillo et al., 2006), 8.1% in Switzerland (Nitsch et al., 2006), 35.8% in Finland (Wasen et al., 2004) and 5.1% in Spain (Otero et al., 2005). The prevalence of CKD was 12.0% in Australia (McDonald et al., 2003).

The prevalence of CKD in China, Thailand and Singapore was found to be 10.8%, 17.5% and 6.6%, respectively (Ingsathit et al., 2010; Shankar et al., 2006; Zhang et al., 2008). In Japan, the prevalence rates of CKD stage 1, 2, 3, 4 and 5 in 2005 was 0.2%, 1.7%, 10.4% and 0.2 %, respectively (Imai et al., 2009).

According to population-based study conducted in West Malaysia (Hooi et al., 2013), the overall prevalence of CKD was 9.07% and the prevalence of CKD stage 1, 2, 3, 4 and 5 was 4.16%, 2.05%, 2.26%, 0.24% and 0.36%, respectively. Furthermore, the

prevalence of end-stage renal disease (ESRD) Malaysian patients on dialysis had risen from 325 (year 2001) to 975 (year 2012) per million populations (pmp) (Lim et al., 2013). The prevalence of CKD varied strongly with age, gender and ethnicity. Moreover, the prevalence estimates of CKD strongly depended on which equation was used for estimating the renal function (Zhang & Rothenbacher, 2008).

1.7.2 Causes of chronic kidney disease

Similar to the etiologies of acute kidney failure, CKD can also be categorized into pre-renal, renal and post-renal causes (Haynes & Winearls, 2010). The identifiable causes of CKD are shown in Table 1.4.

Table 1.4: Identifiable etiologies of chronic kidney disease

Etiologies	Frequent	Less frequent
Pre-renal	Renal arterial disease	
Renal	**Glomerular disease**	**Glomerular disease**
	DN	Amyloidosis
	IgA nephropathy	Vasculitis
	FSGS	Hemolytic-uremia syndrome
	TIN	**TIN**
	PKD	Analgesic nephropathy
	RN	Renal myeloma
Post-renal	**Obstruction**	**Obstruction**
	Prostatic	Retroperitoneal fibrosis

Adapted from Haynes & Winearls (2010); DN-diabetic nephropathy; IgA-immunoglobulin A; FSGS-focal segmental glomerulosclerosis; TIN-tubulointerstitial nephritis; RN-reflux nephropathy; PKD-polycystic kidney disease

As described in Table 1.4, glomerular diseases such as diabetic nephropathy, immunoglobulin A nephropathy (most common glomerulonephritis which causes CKD), focal segmental glomerulosclerosis, and tubulointerstitial nephritis are the

frequent renal causes of CKD. Moreover, renal arterial disease and obstruction due to prostate enlargement are the common pre-renal and post-renal etiologies of CKD

1.8 Burden of chronic kidney disease

1.8.1 Morbidity

CKD is a growing public health problem across the world (Sakhuja & Kohli, 2006). The global annual growth rate of CKD is 8% (Alebiosu & Ayodele, 2005) while the annual dialysis growth rates are 6-8% per annum (Levin, 2003). Statistics from the United States advocated that for each patient with end-stage renal disease (ESRD), there are more than 200 with overt CKD (stage 3 or 4) and nearly 5000 with furtive disease (stage 1 or 2) (Barsoum, 2006).

1.8.2 Mortality

Disease of Genitourinary System is the 12^{th} and 17^{th} cause of mortality and disability worldwide, respectively (Schieppati & Remuzzi, 2005). In United States (US), kidney disease is the 8^{th} leading cause of mortality (Centers for Disease Control and Prevention, 2009).

1.8.3 Economic burden

The cost of medical care in US was 1.7 times greater in patients suffering from CKD stage 3 and 2.6 times greater in CKD stage 4 sufferers compared with controls (Smith et al., 2004). In US, the free-for-service Medicare expenditures per person per year were $87,945 and $71,630 for hemodialysis (HD) and peritoneal dialysis (PD) population, respectively (United States Renal Data System, 2013). The cost of

hemodialysis (HD) treatment in Malaysia ranged from RM79.61-475.79 (mean cost of RM169 per HD) while the mean cost of continuous ambulatory peritoneal dialysis (CAPD) was RM2186 per month (US $1 = RM 3.80) (Hooi et al., 2005). Furthermore, the cost of erythropoietin for HD and CAPD was RM4500 and RM2500 per year, respectively. The abovementioned findings demonstrate that CKD has an enormous socio-economic burden on the healthcare system.

1.9 Co-morbidities among chronic kidney patients

Patients with CKD are known to suffer from various co-morbidities, complications and sequelae as a cause or consequence of renal disease (Bailie et al., 2005). The common co-morbidities of CKD include hypertension (HPT), diabetes mellitus (DM), cardiovascular disease (CVD), anemia, kidney stones, and disorders of mineral and bone metabolism.

1.9.1 Hypertension

Hypertension is the persistent elevated blood pressure (BP) > 140/90 mmHg (Chobanian et al., 2003). The classification of BP for adults 18 years and older is provided in Table 1.5.

Table 1.5: Classification of blood pressure

Classification	Systolic blood pressure mm Hg	Diastolic blood pressure mm Hg
Normal	< 120	< 80
Prehypertension	120-139	80-89
Hypertension	≥ 140	≥ 90
Stage 1	140-159	90-99
Stage 2	≥ 160	≥ 100

Adapted from Chobanian et al. (2003)

Approximately 80% of CKD patients have HPT and it is an imperative risk factor not only to renal disease progression towards end-stage renal failure (ESRF) but also to cardiovascular events (Toto, 2005). Since it is a chronic lifestyle disease, so, the principal approaches to retard the progression of kidney deterioration are through intensive management of HPT and optimization of BP control. These approaches can either be non-pharmacological or pharmacological. Non-pharmacological approaches for the management of HPT included the education of patients regarding lifestyle modification such as weight reduction, Diet, smoking cessation, Physical activity, moderate alcohol consumption, dietary sodium restriction (Martin, 2008). The pharmacological approaches for the treatment of HPT include the use of single or combination of anti-hypertensive medications.

1.9.2 Diabetes mellitus

According to Kidney Early Evaluation Program (KEEP), diabetes mellitus (DM) is a condition in which fasting blood sugar level is > 7 mmol/L or non-fasting blood glucose level ≥ 11 mmol/L (Whaley-Connell et al., 2008). DM is categorized into four classes namely type 1 DM (resulting from β cells destruction leading to absolute insulin deficiency), type 2 DM (consequence of progressive insulin secretory defect), gestational DM and other specific types of DM such as birth defects and chemical induced diabetes (American Diabetes Association, 2011).

The prevalence of DM in CKD population of US was 28.0% (Whaley-Connell et al., 2008) whereas it was 40.8% (Martínez-Castelao et al., 2011) and 62.3% (Al-Ramahi, 2012) in the Spanish and Malaysian CKD population, respectively. Diabetic

nephropathy occurs as a result of the interplay of metabolic and hemodynamic pathways in the renal microcirculation (Figure 1.1) (Cooper et al., 1997).

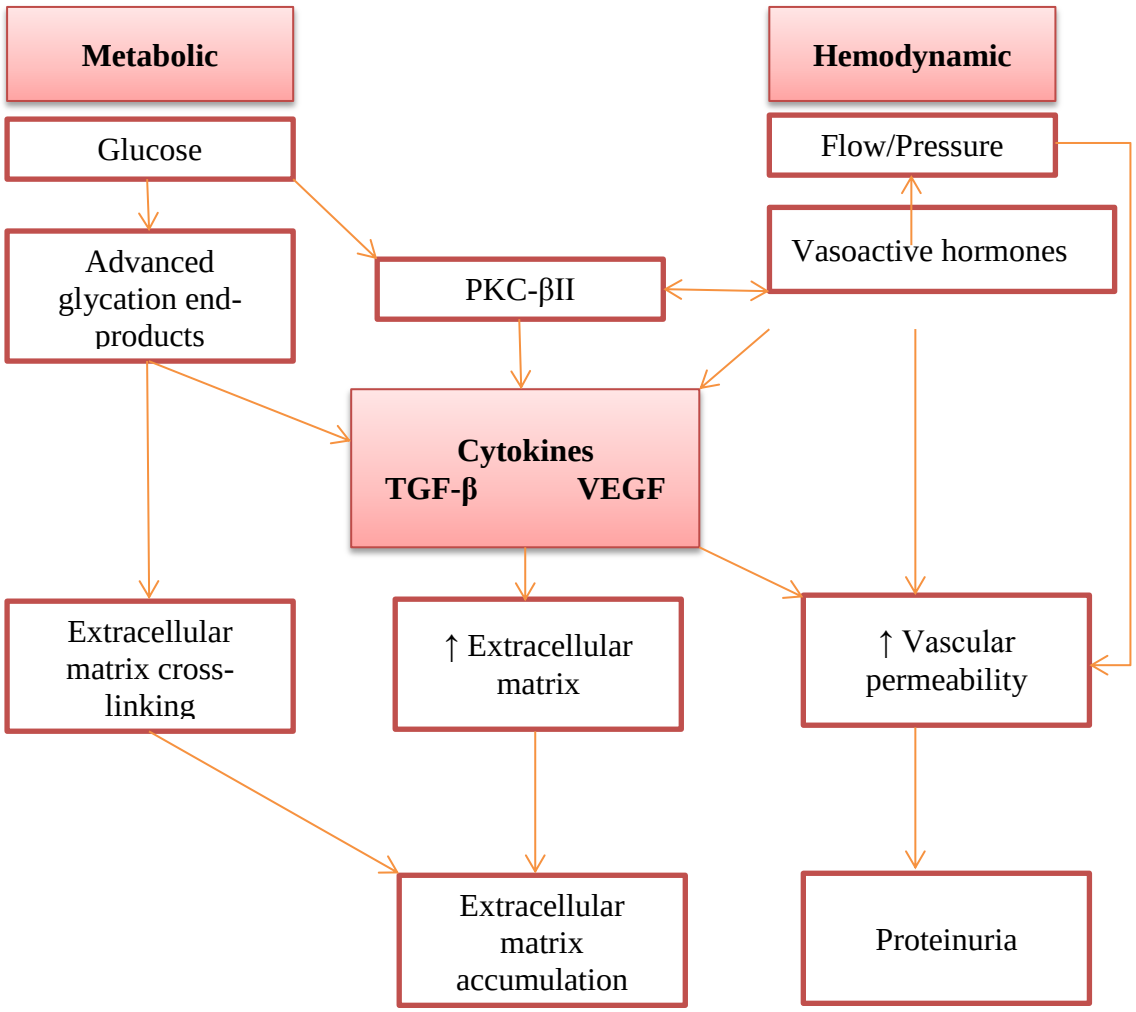

Figure 1.1: Schema outlining potential interactions between metabolic and hemodynamic factors in the pathogenesis of diabetic nephropathy

Adapted from Cooper, Jerums, & Gilbert (1997); TGF=transforming growth factor; VEGF=vascular endothelial growth factor; PKC=protein kinase C.

Inhibitors of abovementioned pathways have increased the understanding of the underlying pathogenic pathways and have led to the development of approaches for the treatment of diabetic nephropathy (Mark, 1998). Pathophysiological mechanisms and their putative treatment in diabetic nephropathy are presented in Table 1.6.

Table 1.6: Suggested pathophysiological pathways and their putative treatment in diabetic nephropathy

Mechanism	Treatment
Metabolic	
Hyperglycemia	Insulin
Increased glucose-derived proteins (e.g. AGE)	Aminoguanidine Advanced glycated endproducts (e.g. PTB)
Polyol	Aldose reductase inhibitors
Mechanical/hormonal	
Elevated systemic blood pressure	Antihypertensive agents
Increased intraglomerular pressure	ACE inhibition, low protein diet
Increased vasoactive hormones	ACE inhibition, angiotensin-II antagonists , ET antagonists
Intermediate pathways	
Growth factors e.g. TGFβ, IGF	Antibodies
Protein kinase C dependent	PKCβ inhibitors

Adapted from Cooper (1998); AGE-advanced glycated endproducts; ACE-angiotensin converting enzyme; IGF-insulin like growth factor; TGF-transforming growth factor; ET-endothelin; PTB-phenacylthiazolium bromide; PKC-protein kinase C

1.9.3 Cardiovascular disease

Cardiovascular disease (CVD) is the principal outcome of CKD and the most frequent cause of mortality in advance stages of CKD (Levey et al., 2003). Nearly half of the overall mortality in CKD patients is associated with CVD (Haynes & Winearls, 2010). Moreover, cardiovascular mortality in CKD population is 10-20 times greater than normotensive population (Foley et al., 1998). The risk rate of cardiovascular mortality was 32 deaths/1000 person-years in patients with CKD compared to 16/1000 person-years among those without CKD (Shlipak et al., 2005). Therefore, CKD is considered as a risk factor of CVD. Moreover, anemia, HPT, DM and mineral bone disease are also the predictors of CVD (Haynes & Winearls, 2010).

1.9.4 Anemia

Anemia is defined as serum hemoglobin < 13.0 g/dL in males and < 12 g/dL in females (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2012). Anemia is a sequela of CKD which occurs as a result of interference of erythropoietin (EPO) production responsible to stimulate bone marrow for production of red blood cells (Singh et al., 2006). Moreover, other factors such as iron and vitamin deficiency, blood loss, decreased life span of erythrocytes, and chronic inflammation also play contributory role in the development of renal anemia (Nurko, 2006). Recent data suggest that anemia is an independent risk factor of adverse cardiovascular outcomes (Sarnak et al., 2002) and combination of anemia and CKD was associated with significantly higher stroke risk (Abramson et al., 2003). The prevalence of anemia is less than 10% in CKD stage 1 and 2, 20-40% in CKD stage 3, 50-60% in stage 4 CKD and more than 70% in stage 5 CKD which reflects that prevalence of anemia increases with declining kidney function (Lankhorst & Wish, 2010).

1.9.5 Kidney stones

Kidney stones are the risk factor of CKD as the prevalence of CKD was higher in stone formers (6.9%) than normotensive subjects (3.1%) (Rule et al., 2009). A previous study surveyed the history of kidney stones in 300 African Americans and compared their results with the 5341 African Americans who participated in National Health and Nutrition Examination Survey III and found out that the self-reported history of kidney stones was higher in ESRD patients (8%) as compared to the population controlled subjects (3%) (Stankus et al., 2007). The mechanism through

which kidney stones cause CKD is mainly attributed either to an obstructive uropathy or pyelonephritis (Rule et al., 2011).

1.9.6 Chronic kidney disease-Mineral and bone disorders (CKD-MBD)

A progressive worsening in mineral homeostasis occurs when renal function decreases, with abnormalities of phosphorus and calcium concentrations, and disruptions of hormones levels including parathyroid hormone, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and other metabolites of vitamin D, fibroblast growth factor-23, and growth hormone. Starting from CKD stage 3, kidneys ability to eliminate phosphate load is reduced, causing hyperphosphatemia, higher Parathyroid hormone, and diminished 1,25-dihydroxyvitamin D with associated increase in fibroblast growth factor levels. There is a decreased intestinal absorption of calcium and increased parathyroid hormone due to the impaired conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. The kidneys do not respond sufficiently to PTH, which promotes the excretion of phosphate and reabsorption of calcium (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2009). CKD-MBD is defined as a systemic disorder of mineral and bone metabolism because of CKD indicated by either one or combination of following (Moe et al., 2006);

- Abnormalities of calcium, phosphorus, parathyroid hormone levels, or vitamin D metabolism
- Anomalies of bone turnover, mineralization, linear growth, volume, or strength
- Vascular calcification

The abnormalities of calcium, phosphorus and parathyroid hormone are associated with vascular calcification and cardiovascular events particularly in patients with advanced CKD (Toussaint et al., 2011).

1.9 Consequences of Chronic kidney disease

Renal failure is traditionally regarded as the most serious outcome of CKD (Levey & Coresh, 2012). Other outcomes of CKD are the complications of declined GFR, higher risk of CVD, acute renal injury, cognitive impairment, infections and impaired physical function (Hailpern et al., 2007; C. Hsu et al., 2008; James et al., 2010; James et al., 2009; Wilhelm-Leen et al., 2009). Complications can occur at any stage of CKD which often lead to death without progression to kidney failure (Levey & Coresh, 2012).

Keith et al., (2004) reported that the rate of RRT over the 5-year (1996-2001) observation period was 1.1%, 1.3%, and 19.9%, respectively, for the CKD stages 2, 3, and 4, but that the mortality rate was 19.5%, 24.3%, and 45.7%. Thus, death was far more common than dialysis at all stages. Go et al., (2004) reported that the risk of death increased as the GFR decreased below 60 ml/min/1.73m^2: the adjusted hazard ratio for death was 1.2 with an estimated GFR of 45-59 ml/min/1.73m^2, 1.8 with estimated GFR of 30-44 ml/min/1.73m^2, 3.2 with an estimated GFR of 15-29 ml/min/1.73m^2, and 5.9 with an estimated GFR < 15 ml/min/1.73m^2. Furthermore, the adjusted hazard ratio for cardiovascular events also increased inversely with the estimated GFR.

Kurella et al., (2004) found that there was a graded relation between cognitive function and severity of CKD. Mean scores of Modified Mini-Mental State Examination (3MS), Trailmaking Test B (Trails B), and California Verbal Learning Trial (CVLT) immediate and delayed recall were worse for ESRD patients than CKD patients or published norms ($p < 0.001$ for all comparisons). Moreover, the scores on the Trails B ($p < 0.001$) and CVLT immediate ($p = 0.01$) and delayed ($p < 0.001$) recall were significantly worse for subjects with CKD not requiring dialysis than for published norms.

CHAPTER 2

LITERATURE REVIEW

This chapter contains the review of literature. Moreover, it also includes rationale and aims of the study which are given at the end of this chapter.

2.1 Search strategy

A literature search was conducted on Google Scholar, PubMed, Science direct and ProQuest databases to find all potentially relevant publications before July 2014. The following words were used for current search: "chronic kidney disease", "chronic renal failure", "end-stage renal disease", "epidemiology", "etiology", "medication prescribing patterns", and "medication related problems". The reference lists of primary original articles and review articles were also checked so that further relevant studies could be found.

2.2 Study selection

Research articles and review articles that reported either the etiologies/causes of CKD or medication prescribing patterns among CKD patients were included whereas the data published as case reports or in the form of abstracts were excluded due to the insufficiency of information in the abstracts.

2.3 Demographic patterns of chronic kidney disease

A prospective study conducted in 4 nephrology centers of US found that the mean age of pre-dialysis patients was 60.6 ± 16.0 years (61.3 ± 15.8 years in CKD stage 2 and 3, 60.8 ± 16.6 years in CKD stage 4 and 59.1 ± 14.1 years in CKD stage 5). Moreover, men were more likely to have CKD as compared to female (66% vs 44%) and the prevalence of CKD stages 2 and 3, 4 and 5 was 24.2%, 56.5% and 18.7%, respectively. The most common comorbidity was hypertension followed by diabetes. They suggested increasing the screening programs for the early detection of individuals with CKD or risk of CKD development (Bailie et al., 2005).

Martinez-Castelao et al. (2011) conducted a prospective study on Spanish cohort of CKD stage 3 and 4 patients. The mean age of their cohort was 68 ± 13 years and there was no significant difference of age between CKD stages. Moreover, they observed a preponderance of male and overweight patients. They revealed that the prevalence of hypertension was universal among CKD stages whereas the prevalence of CVD increased significantly by declining renal function with the hierarchy (stage 3a < stage 3b < stage 4).

Gooneratne et al., (2006) carried out a descriptive hospital-based 3-month study at National Hospital of Sri Lanka. They recruited 121 patients with male to female ratio being 2.5:1. The mean age of the patients was 47.8 years (range 20-83) and there was predominance of Sinhalese (75.2%) and patients from Western province (57%). The percentage of patients with CKD stage 3, 4, 5 and acute on chronic kidney disease was 3.3%, 4.1%, 66.9% and 5%, respectively. The stage of CKD was unknown or undetermined in 20.7% of their cohort.

A prospective study conducted in Penang General Hospital, Malaysia revealed that the mean age of the patients was 55.56 ± 14.15 years and there was majority of the male CKD patients and Chinese race. The prevalence of CKD stage 3, 4 and 5 was 3.7%, 7.7% and 88.7%, respectively. The common comorbidities were anemia (87.3%), hypertension (80.0%) and diabetes mellitus (62.3%) (Al-Ramahi, 2012).

2.4 Trends of known and unknown etiologies of chronic kidney disease

Etiologies of CKD vary from country to country but diabetes and HPT are the foremost etiologies of CKD in all developed and several developing countries while glomerulonephritis (GN) and unknown etiology are more frequent causes of CKD in Asian and African countries (Jha et al., 2013). These variances are associated to the disease burden moving away from infections towards diseases of longevity, reduced birth rates, and higher life expectancy in developed nations (Ayodele & Alebiosu, 2010). On the contrary, infectious diseases (e.g. pyelonephritis, post-streptococcal GN etc.) remain to be more prevalent in low economic countries due to poor sanitation, insufficient supply of safe water and greater concentrations of disease-transmitting vectors (Engelgau, 2011).

According to the United States Renal Data System (2013) report, diabetic nephropathy was the leading etiology of ESRD followed by HPT while glomerular diseases and adult polycystic kidney disease (APKD) were among the less frequent causes. Major known causes of ESRD in New Zealand and Australia were DN (49% and 36%, respectively), GN (20% and 19%, respectively), HPT (9% and 12%, respectively) while unknown etiology was 3% and 6%, respectively (Grace, McDonald, Hurst, & Clayton, 2013). The etiologies of ESRD reported in European

and some other countries are depicted in Figure 2.1 (European Renal Association-European Dialysis and Transplant Association, 2013). Diabetes and HPT are the leading causes of kidney failure in majority of the European nations. The incidence of renal failure due to diabetes and hypertension ranged from 12.6-50.0 % and 2.3-30.0 %, respectively. On the other hand, GN is the foremost etiology of ESRF in Russia, Albania and Ukraine. The incidence of kidney failure due to unknown etiology ranged from 0-22.9% (Figure 2.1).

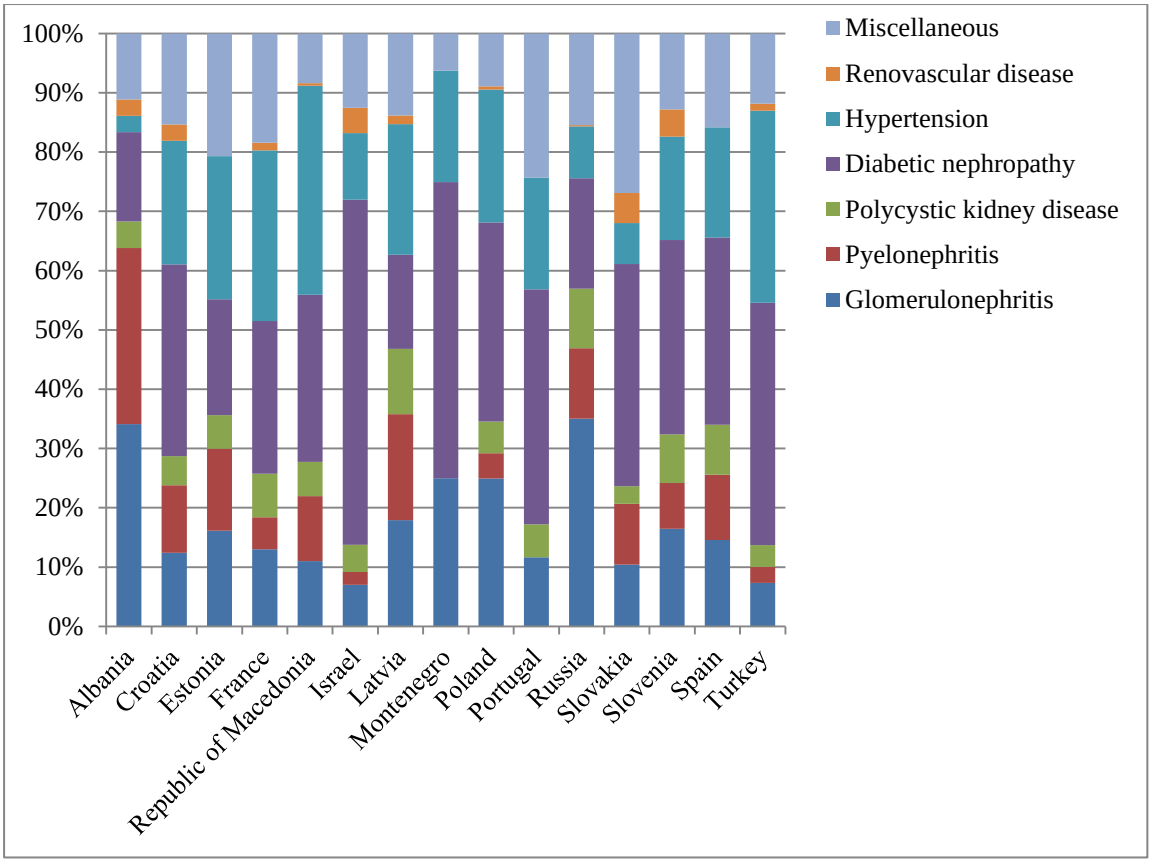

Figure 2.1 Etiologies of end-stage renal disease in European and some other countries

A retrospective study conducted on 182 chronic renal failure (CRF) patients at a Nigerian tertiary care institute revealed that chronic glomerulonephritis (CGN) (41.2%) was the commonest cause of CRF followed by hypertensive nephrosclerosis

(26.1%) and DN (13.1%) (Alebiosu et al., 2006). To highlight the burden of CKD, another study was carried out in south-east Nigerian tertiary care setting, involving 1538 ESRD patients which demonstrated that 86.5% of their patients were less than 60 years old and the cause of ESRD was uncertain in more than half of the patients while the leading identifiable causes were HPT and GN accounted in 17.6% and 14.6% of their study participants (Ulasi & Ijoma, 2010). In another epidemiological study involving 800 ESRD Egyptian patients, the known etiologies of ESRD were HPT (20%), obstructive uropathy (OBS) (12%), CGN (11%), diabetic nephropathy (DN) (8%), chronic pyelonephritis (CPN) (5%), analgesic nephropathy (5%), bilhaziasis (3%) and lupus nephritis (9%) while cause of ESRD was unknown in majority of their patients (27.1%) (El Minshawy, 2011).

The most frequent cause of CRF in Yemen was GN (25.4%), followed by OBS (13.7%), HPT and pyelonephritis (11.8% each), DN (7.8%) and the less frequent causes were malaria, arthritis, postpartum hemorrhage, vasculitis, and Alport's syndrome (Badheeb, 2006). According to a study conducted on 248 HD patients in Jeddah (Kingdom of Saudi Arabia) to investigate the causes of ESRD found that the majority of their ESRD cases were of unknown cause (42.7%) and HPT was the commonest identifiable cause followed by DN (Al-Jiffri & Fadag, 2003). Similarly, a retrospective medical records review of 1357 ESRD Saudi patients showed that the most common known causes of ESRD were HPT (45.9%) followed by DN (17.7%) and Glomerular diseases (15.8%) (Maimini et al., 2012). Moreover, the percentage of ESRD patients due to unknown cause in the abovementioned study was 1%. On the contrary, a prospective study of incident ESRD patients in Madinah (Kingdom of Saudi Arabia) indicated that the leading known cause of ESRD was DN (42.5%) and