The University of Nottingham

Epidemiology of Dialysis-Treated End-Stage Kidney Disease in Adults in Libya

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To my family,

with all my love

Abstract

Background: The extent and the distribution of end stage kidney disease (ESKD) in Libya have not been reported despite provision of dialysis over 4 decades. The aim of this thesis is to develop the first comprehensive description of the epidemiology of dialysis-treated ESKD in adults in Libya as well as to assess the outcomes of this treatment.

Methods: A structured interview regarding dialysis provision and infection control measures was conducted with the medical directors of all 40 dialysis centres and 28 centres were visited. In the same time demographic and clinical data were obtained regarding all adult patients treated at all maintenance dialysis facilities in Libya from May to August 2009. Additional information about the patterns of vascular access used for haemodialysis (HD) as well as prevalence and incidence of hepatitis B and/or C infection was collected and analysed. Subsequently data were collected prospectively from September 2009 to August 2010.

Results: There were 40 functioning maintenance dialysis centres in Libya (one of them was serving children only). The total number of adult patients was 2417. The prevalence rate of ESKD treated by dialysis was 624 per million population. Most dialysis units were located in the northern part of the country and only 12.5% were free standing units. Only three centres offered peritoneal dialysis. There were 192 HD rooms. They hosted 713 functioning HD stations, giving a ratio of one machine to 3.4 patients. Nephrologist/internist to patient ratio was 1:40 and nurse to patient ratio was 1:3.7. There was wide variation in monitoring of dialysis patients with dialysis adequacy assessed only in a minority. 85% of prevalent patients were aged <65 years and 58% were male. The prevalence of ESKD varied considerably with age with a peak at 55-64 years (2475 pmp for males; 2197 pmp for females). The annual incidence rate was 282 pmp with some regional variation and a substantially higher rate in the South (617 pmp). The most common cause of ESKD among prevalent and incident patients was diabetes. Other important causes were glomerulonephritis, hypertensive nephropathy and congenital or hereditary diseases. During one year follow- up, 458 deaths occurred, (crude annual mortality rate of 21.2%). Of these, 31% were due to ischaemic heart disease, 16% cerebrovascular accidents and 16% due to infection. Annual mortality rate was 0-70% in

different dialysis centres. Best survival was in age group 25-34 years. Binary logistic regression analysis identified age at onset of dialysis, physical dependency, diabetes and predialysis urea as independent determinants of increased mortality. Of all dialysis- treated patients, 34.9% were sero-positive for HBV and/or HCV (anti-HCV positive 31.1%; HBsAg positive 2.6%; both positive 1.2%). The prevalence of HBV±HCV infection varied widely between HD centres from 0% to 75.9%. Sero-positive patients were younger, had longer time on dialysis and more previous blood transfusions. Prospective follow-up revealed an incidence of sero-conversion of 7.7% during 1 year (7.1% HCV; 0.6% HBV). Wide variation in rates of newly acquired infections was observed between dialysis centres. Duration of dialysis, history of previous renal transplant and history of receiving HD in another centre in Libya were significantly associated with sero-conversion. The majority of HD- treated patients (91.9%; n=1573) were using permanent vascular access in the form of arteriovenous fistula or arteriovenous graft. Patients with permanent vascular access were more likely to be male and less likely to be diabetic. Most patients had commenced HD using a temporary central venous catheter (91.8%). Vascular access- related complications were: thrombosis (46.7%), aneurysm (22.6%), infection (11.5%) and haemorrhage (10.2%). Hospitalisation for VA related complications was reported by 31.4%.

Conclusion: ESKD in Libya is a major health problem where the incidence rate is among the highest in the world. Despite rapid expansion of dialysis services throughout the country, this thesis has identified that many aspects of dialysis provision are suboptimal and that outcomes are relatively poor. We have identified several major challenges to improving the quality of dialysis provision including lack of dialysis practice guidelines, absence of auditing and quality control and limited access to kidney transplantation. As Libya reorganises its health services in the post-conflict period it is hoped that this study will be the first step in establishing a renal registry and that the areas of concern highlighted will prompt the implementation of national clinical practice guidelines for dialysis.

Publications and abstracts arising from this thesis

Peer reviewed publications

- Alashek WA, McIntyre CW, Taal MW. Provision and quality of dialysis services in Libya. *Hemodial Int.* 2011 Oct;15(4):444-52.
- Alashek WA, McIntyre CW, Taal MW. Epidemiology and aetiology of dialysis-treated end-stage kidney disease in Libya. *BMC Nephrol.* 2012 Jun 8;13:33.
- Alashek WA, McIntyre CW, Taal MW. Hepatitis B and C infection in haemodialysis patients in Libya: Prevalence, Incidence and Risk Factors. *BMC Infectious Disease.* 2012; 12: 265
- Alashek WA, McIntyre CW, Taal MW. Vascular Access in Patients Receiving Haemodialysis in Libya. *J Vasc Access.* 2012 Jul 27:0. doi: 10.5301/jva.5000089.
- Alashek WA, McIntyre CW, Taal MW. Determinants of survival in patients receiving dialysis in Libya. *Hemodial Int.* 2012 Aug 13. doi: 10.1111/j.1542-4758.2012.00728.x.

Oral presentation

- Alashek WA, McIntyre CW, Taal MW, Mammi MM. Hepatitis C virus in Libya's haemodialysis centres: Prevalence rates and transmission factors. AMDI-International Biohealth Science Conference 2010. Penang, Malaysia, 29th Nov 2010.

Poster presentations

- Alashek WA, McIntyre CW, Taal MW. Medical assessment of haemodialysis patients in Libya. British Renal Society/ Renal Association, Manchester, United Kingdom, 17th May 2010 (abstract ref: P327).

- Alashek WA, McIntyre CW, Taal MW. Characteristics of dialysis services in Libya. British Renal Society/ Renal Association, Manchester, United Kingdom, 17th May 2010 (abstract ref: P328).
- Alashek WA, McIntyre CW, Taal MW, Buargub, MB, BenOmran MM, Aboudhair MA. Presentation of diabetic end-stage kidney disease to haemodialysis in Libya. The Libyan Association for Diabetes and Endocrinology, Benghazi, Libya. Ibnosina Journal of Medicine and Biomedical Sciences (2010).
- Alashek WA, McIntyre CW, Taal MW. Morbidity of diabetic end-stage kidney disease patients treated by dialysis in Libya. International Diabetes and Obesity Forum, Athens, Greece, 2 1st October 2010 (abstract ref: PP060).
- Alashek WA, McIntyre CW, Taal MW. Dialysis in Libya: Patients and service provision. World Congress of Nephrology 2011, Vancouver, Canada, 8th April 2011 (abstract ref: SA454/841).
- Alashek WA, McIntyre CW, Taal MW, Fluck RJ. High utilisation of arteriovenous fistulas in haemodialysis patients is still possible despite limited access to surgical services and low pre-dialysis formation rates. British Renal Society/ Renal Association, Birmingham, United Kingdom, 6th June 2011 (abstract ref: B17).
- Alashek WA, McIntyre CW, Taal MW. Blood- bourne virus infection in Libya's dialysis centres: Prevalence and risk factors. British Renal Society/ Renal Association, Birmingham, United Kingdom, 6th June 2011 (abstract ref: H9).
- Alashek WA, McIntyre CW, Taal MW. Determinants of survival in adult dialysis patients in Libya. British Renal Society, Manchester, United Kingdom, 1st May 2012 (abstract ref: P104).

Declaration

I declare that the thesis described herein is entirely my own work with assistance as indicated in the acknowledgements and is based upon research carried out in Libya and supervised by the Department of Vascular Medicine, School of Graduate Entry Medicine and Health, University of Nottingham between May 2009 and September 2012.

Wiam A. Alashek

September 2012.

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During my research and preparation of this thesis I have worked with a great number of people whose involvement in different ways deserves special mention. In the first place, I would like to record my gratitude to my supervisors; Prof Chris McIntyre and Dr Maarten Taal who were always there with advice, guidance, encouragement and challenging queries, giving me extraordinary experiences throughout the study.

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It is a pleasure to pay tribute also to the medical graduates who participated in data collection from maintenance dialysis facilities in different cities in Libya as well as the medical researcher appointed by the Libyan National Authority for Scientific Research for their assistance in gathering data needed for this research.

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Finally, words fail me to express my appreciation to my family for their unconditional support during my PhD years.

Contents

List of Figures

Abbreviations

AVF	Arteriovenous fistula
AVG	Arteriovenous graft
CAPD	Continuous ambulatory peritoneal dialysis
CKD	Chronic kidney disease
CVC	Central venous catheter
Dopps	Dialysis outcome and practice patterns study
ELISA	Enzyme-linked immunosorbent assay
ERA-EDTA	European Renal Association–European Dialysis and Transplant Association
ESKD	End-stage kidney disease
GFR	Glomerular filtration rate
HBV	Hepatitis B Virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HD	Haemodialysis
ISHCOF	The international study of health care organisation and financing
KDOQI	Kidney Disease Outcomes Quality Initiative
NKF	National kidney foundation
PCR	Polymerase chain reaction
PD	Peritoneal dialysis
PHC	Primary health care
pmp	per million population
RRT	Renal replacement therapy
USRDS	United States Renal Data System

Chapter 1

Introduction

1. Introduction

1.1. End-Stage Kidney Disease

End-stage kidney disease (ESKD) refers operationally to the advanced and irreversible loss of kidney function which necessities treatment with maintenance dialysis (haemodialysis (HD) or peritoneal dialysis (PD)) or kidney transplantation. Scientifically, it is defined as the failure or near failure of the kidneys to perform their normal functions, which include excretion of metabolites, maintenance of acid-base status, fluid and electrolyte balance and the synthesis of hormones such as erythropoietin and rennin (1, 2). ESKD is usually the end result of a progressive Chronic Kidney Disease (CKD) and gradual loss of renal function. Occasionally, it is the result of a rapidly progressive disease of sudden onset. Few symptoms develop until more than 75% of glomerular filtration is lost. Symptoms worsen as kidney function decreases beyond this level. If the condition continues unchecked, uremic toxins accumulate and produce potentially fatal physiologic changes in all major organ systems.

The term ESKD corresponds with CKD stage 5. The Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) in the United States provided evidence-based clinical practice guidelines for all stages of CKD and related complications in 2002. ESKD is defined as glomerular filtration rate (GFR) of less than 15 ml/min/1.73m^2 body surface area, irrespective of the underlying aetiology of the kidney damage (1).

The GFR is considered the best measure of overall kidney function (3, 4). Normal GFR varies according to age, sex and body size. In young adults, the normal GFR is approximately 120 to 130 mL per minute per 1.73 m^2 and declines with age (1, 4). The NKF/KDOQI working group defined CKD in adults as:

- Kidney damage for $\geq$3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either pathological abnormalities, or markers of kidney damage, including abnormalities in the composition of blood, urine or imaging tests. Or
- Decreased GFR, with or without evidence of kidney damage.

CKD is further subdivided into five subgroups according to the degree of severity of estimated GFR reduction as described in table 1. 1.

Table 1. 1: Stages of Chronic Kidney Diseases

Glomerular filtration rate ($mL/min/1.73\ m^2$)	Stages	Description
≥90	1	Kidney damage with normal or ↑GFR
60-89	2	Kidney damage with mild ↓GFR
30-59	3	Moderate ↓GFR
15-29	4	Severe ↓GFR
< 15	5	End-Stage Kidney Disease (ESKD)

1.2. Global trends in end-stage kidney disease

The number of patients with ESKD is increasing worldwide as a consequence of the rise in non-communicable diseases. ESKD is a life-long medical condition with profound impact on patients, families and the health care sector. The World Health Report 2002 and Global Burden of Disease project indicated that diseases of the kidney and urinary tract significantly contribute to the global burden of diseases (http://www.who.int/whr/2002/en/). Recently it was estimated that globally over 2 million people require treatment for ESKD to sustain life (5). In reality the number might be 10 fold higher than the estimated figures as the access to renal replacement therapy (RRT) is restricted or not available in over 112 countries and many patients die before having access to diagnostic and therapeutic health services (6-9). Consequently, it has been estimated that worldwide more than a million people die every year from ESKD. Moreover, management of ESKD is a major cost pressure even in countries that

can afford it. These factors render ESKD an important focus of health care planning even in the developed world, but the problems they delineate in the developing world are far more challenging (7).

Trends in ESKD are best studied longitudinally from annual renal registry reports. They provide the best tool for assessing the overall epidemiology of renal diseases in a community and permit international comparison. Renal registries are not established in many countries, where the trends are studied using other observational methods. However, interpreting rates of incidence and prevalence of ESKD across countries is complicated by the lack of uniform data collection methods.

According to the 2011 report of the United States Renal Data System (USRDS) (10), the rates of incident ESKD across the globe show important trends; rates have slowed in some countries, while rising or remaining stable in others. The United States, Taiwan and Japan continue to have some of the highest rates, at 355 per million population (pmp), 347 pmp and 287 pmp in 2009 (figure 1.1).

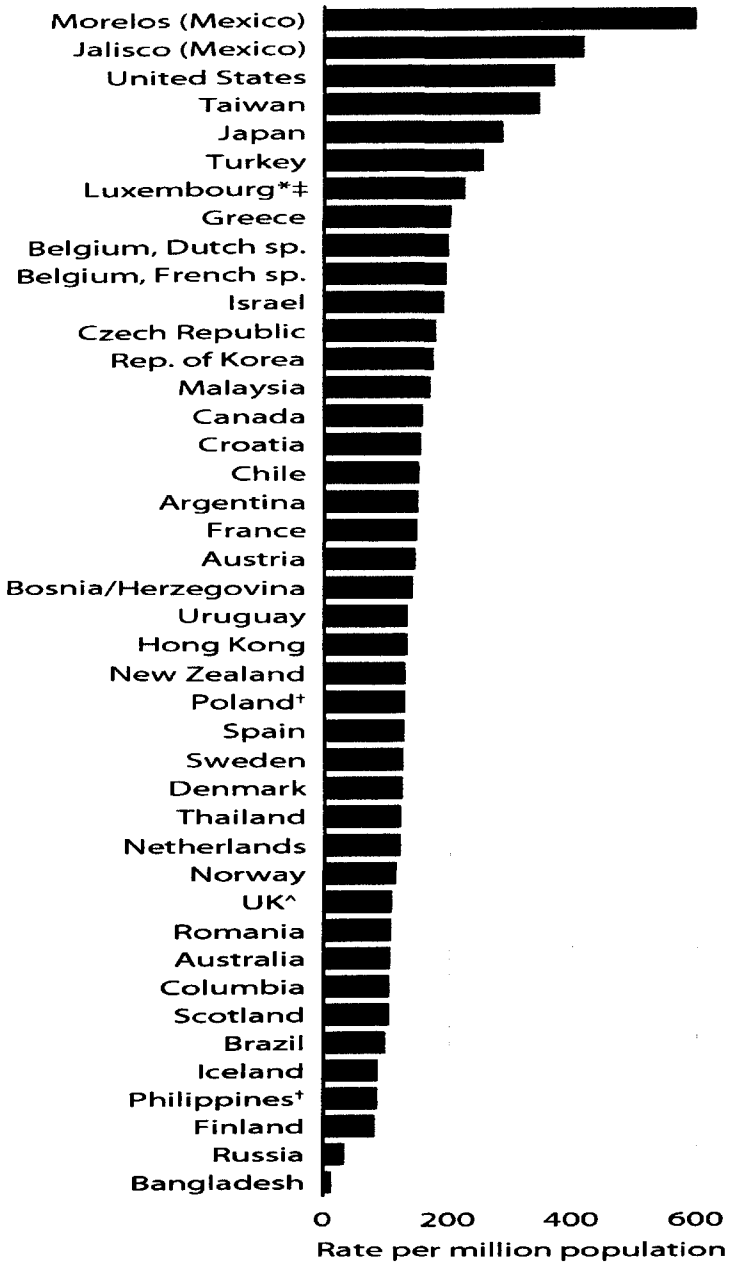

Figure 1. 1: Incidence of ESKD in different countries, 2009- United States Renal Data System (2011)

The annual incidence of ESKD in the United States showed relative stability as compared to data from 2000-2009 (10). This secular trend is quite different from that observed in the 1980s and 1990s during which the incidence of ESKD increased at a rapid rate (10). The annual report of the European Renal Association–European Dialysis and Transplant Association Registry (ERA-EDTA) 2009 (11), which gathers data from many European national registries, showed an overall incidence rate of ESKD among all registries of 122 pmp. It also showed

wide variation in the incidence rates reported by different countries. During 2008, the highest incidence rates were reported by Turkey (264 pmp), Portugal (232 pmp) and Greece (199 pmp), whereas incidence rates below 100 pmp were reported by Ukraine (15 pmp), Montenegro (30 pmp), Russia (37 pmp), Estonia (66 pmp), Iceland (73 pmp), Latvia (95 pmp), Finland (95 pmp) and Romania (96 pmp) (11). Similarly, evaluation of trends from 2004 to 2008 showed minor increases in most countries and levelling off of rates or even a slight decrease in incidence of ESKD. The Thirteenth Annual Report of The UK Renal Registry showed that the incidence rate in the UK during 2009 was stable at 109 pmp and, similarly rates had levelled off in the last three years (12) (figure 1. 2).

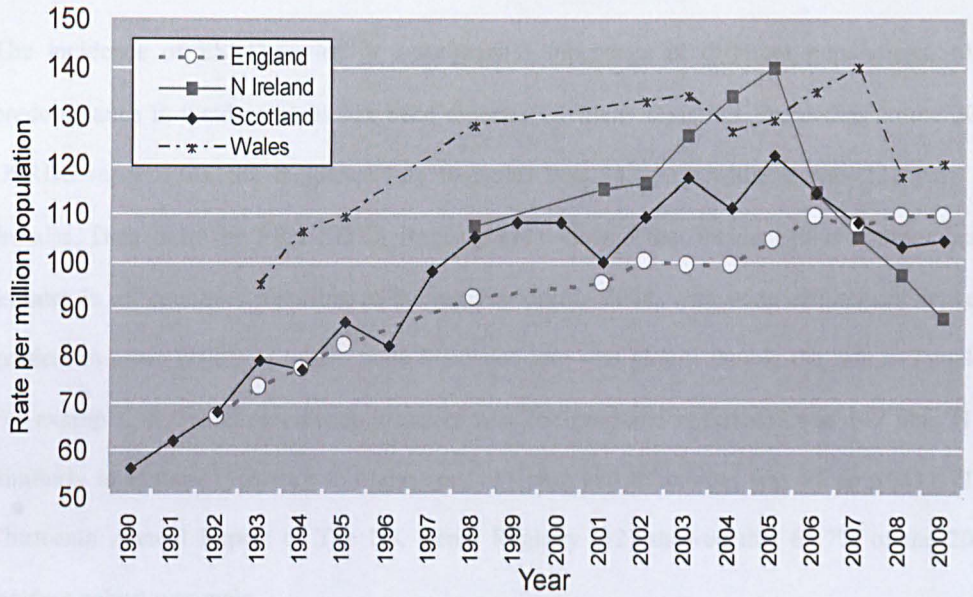

Figure 1. 2: Incidence rates of renal replacement therapy in the countries of the United Kingdom 1990- 2009

Similarly, The Thirty Third Report of the Australia and New Zealand Dialysis and Transplant Registry (2010) (13) showed that the incidence of ESKD in Australia was 107 pmp in 2009, a decrease of 8% from 2008 (119 pmp) when the incidence rate was similar to 2005 (113 pmp). Therefore, most recent reports from developed countries show no change or a small decrease in the rate of new cases. In these countries, success may be attributed to application of preventive

measures including control of blood pressure, better glycemic control and screening of at risk population (14).

Incidence rates reported from the Middle and Far East show variable patterns. The Malaysian Dialysis and Transplant Registry (15) reported an incidence of ESKD treated with dialysis of 170 pmp in 2009 which is approximately as double the rate during 2001 (88 pmp). Reports from other countries in the region depended on small studies rather than well-established renal registries. For instance, the incidence in Qatar was 202 pmp (16), Tunisia (159 pmp) (17), Bhopal city in India (151 pmp) (18), Saudi Arabia (122 pmp) (19), Jordan (111 pmp) (20) and Aleppo city in Syria (60 pmp) (21). However, the long term trend of ESKD incidence in most Middle and Far East countries could not be interpreted in these places due to insufficient information.

The incidence of ESKD varies in demographic subgroups of different populations. Male predominance in incident cases has been reported by many registries. According to the 2011 USRDS report (10), the incidence rate in males was 353 pmp while it was 222 pmp for females. Data from the ERA-EDTA Registry (11) showed that incident males outnumbered females in all countries reporting to the registry during 2008, with wide differences between genders in some countries where male incidence rate was almost double the rate in females. For example, in Greece, incidence in males was 262 pmp and in females was 147 pmp (11). Similarly in Finland incidence in males was 111 pmp and in females was 55 pmp (11). The Thirteenth Annual Report of The UK Renal Registry (12) showed that 61.7% of the 2009 incident cohort was male.

Age is another demographic variable which significantly impacts the incidence of ESKD. The mean age of incident patients with ESKD in developed countries is higher than those in developing nations. According to the 2011 USRDS report (10), the mean age of incident ESKD patients was 62.6 years. Incidence rates increased progressively with increasing age of patients such that it was 131 pmp in those aged 20–44 years and 610 pmp in those aged 45–64 while it reached 1,407 pmp in those aged 65–74years (10) (figure 1. 3).

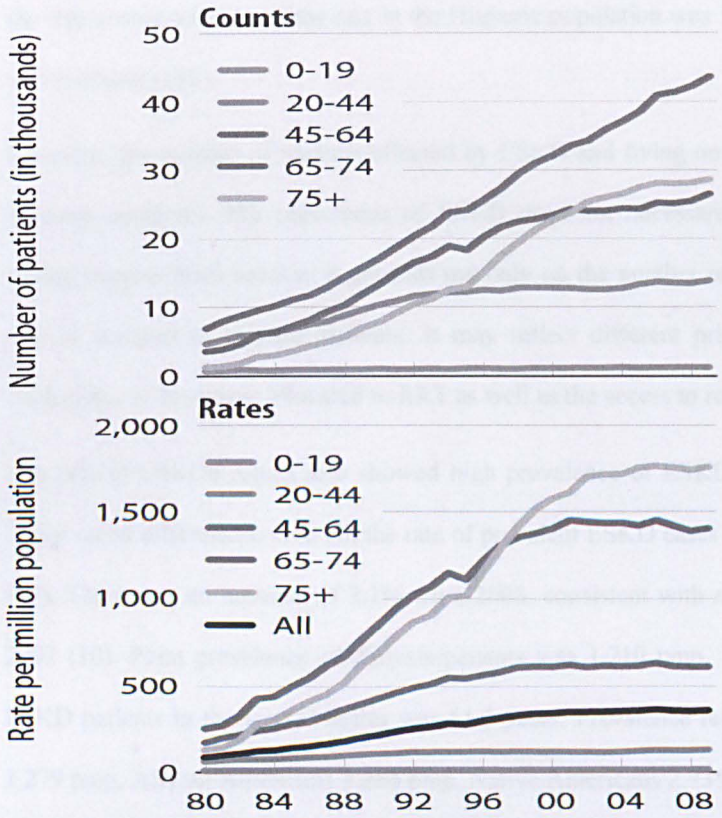

Figure 1. 3: Incident counts and adjusted rates of ESKD, by age, United States Renal Data System (2011)

Data from the ERA-EDTA Registry (11) shows that the mean age of incident patients in 2008 ranged from 44 years in Ukraine to 69 years in Dutch-speaking Belgium. In the UK, the median age was 64.8 years for all incident patients and 57.1 years for non-Whites (12). In Australia, the mean age of incident ESKD patients was 60.7 years and the median was 63.4 years (13). In contrast, the mean age of incident patients in the developing world is generally substantially lower. For instance, the mean age of incident ESKD patients during 2005 in India was 46 years (22). This is likely due to multiple factors including lower population life expectancy, rationing of RRT to younger patients and higher prevalence of kidney diseases that affect younger people.

The incidence of ESKD also varies greatly across patient ethnic subgroups. According to the USRDS (10), the incidence in White Americans was 277 pmp, African Americans 976 pmp, Native Americans 523 pmp and Asian Americans 403 pmp. The incident rates in the African American and Native American populations were 3.5 and 1.9 times greater, respectively, than

the rate among whites and the rate in the Hispanic population was 1.5 times higher than that of non-Hispanics (10).

Likewise, the number of patients affected by ESKD and living on RRT shows wide variation between countries. The prevalence of ESKD does not necessarily reflect the health status among communities because it depends not only on the number of new cases but also on the rate of survival of existing patients. It may reflect different priorities for health care and inadequacy of resources allocated to RRT as well as the access to renal transplantation.

The (2011) USRDS report also showed high prevalence of ESKD in the United States with major racial differences. Overall, the rate of prevalent ESKD cases reached 1,738 pmp in 2009 (10). There was an increase of 2.1% from 2008, consistent with a similar rise per year since 2002 (10). Point prevalence of dialysis patients was 1,210 pmp. The mean age of prevalent ESKD patients in the United States was 61.1 years. Prevalence rate in White Americans was 1,279 pmp, African Americans 5,284 pmp, Native Americans 2,735 pmp and Asian Americans 2,101 pmp (10).

International data reported from different registries in the world showed that Taiwan and Japan continue to report the highest rates of prevalent ESKD, at 2,447 and 2,205 pmp, respectively, in 2009 (10). High prevalence rates were also reported by Jalisco (Mexico) and French-speaking as well as Dutch-speaking Belgium, at 1,314 pmp, 1,193 pmp and 1,141 pmp, respectively (10). The lowest rates were reported by Bangladesh and the Philippines, at 140 pmp and 110 pmp (10).

The overall prevalence among all registries reporting to the ERA-EDTA Registry in 2008 was 644 pmp (11). The highest prevalence was in Portugal (1408 pmp), Belgium (French-speaking) (1153 pmp) and Spain (Catalonia) (1124 pmp). The lowest prevalence was reported by Ukraine (89 pmp) and Russia (165 pmp). The Thirteenth Annual Report of The UK Renal Registry (23) showed that the prevalence rate of ESKD was 417 pmp and the median age of prevalent patients was 57.7 years. There were a gradual growth in the prevalence of dialysis population by 3.5 pmp between 2005 and 2009. It also showed that prevalence rates in males exceeded those in females; the peak for males was in the 75–79 year age group at 2,632 pmp and for females the peak was in the 70–74 year age group at 1,445 pmp (23). The prevalence rate of

dialysis in Australia had showed almost similar rate (473 pmp) (13). New Zealand showed higher prevalence rate of dialysis (524 pmp) (13) while in Malaysia it was 762 pmp (15).

The prevalence rates for the Mediterranean region were estimated to range between 312 to 352 pmp (24, 25). Other reports from individual countries in the region showed variable prevalences including Saudi Arabia (475 pmp) (19), El-Minia city in Egypt (208 pmp) (26), Kuwait (240 pmp) (24) and Oman (220 pmp) (24).

1.3. Aetiology of end-stage kidney disease

Kidney damage may result from a multitude of primary kidney disorders or systemic diseases. Some factors play a role in initiating the disease in individuals and other factors drive the progression of the condition among those with established CKD. If the cause of CKD is not determined relatively early in its course the primary diagnosis may be difficult to discern. Generally, causes of ESKD in a population are influenced by the effect of demographic variables including gender, ethnicity and socioeconomic status.

Diabetes and hypertension account together for almost 60% of ESKD (10). Diabetic nephropathy is rapidly becoming the single most common cause for ESKD worldwide as the prevalence of diabetes is increasing progressively in most countries. Over the past 25 years, the prevalence of type 2 diabetes has almost doubled in the United States, increased three- to five fold in India, Indonesia, China, Korea and Thailand (27, 28). Diabetes is extremely frequent in the Middle East countries. The International Diabetes Federation (http://www.idf.org/diabetesatlas/) ranked Kuwait, Lebanon, Qatar, Saudi Arabia, Bahrain and the United Arab Emirates among the countries with highest prevalence of diabetes in the world. Several studies have shown that diabetes is associated with a substantially increased risk of ESKD (29-32). Researchers estimated that almost 40% of diabetic patients will develop CKD within 10 years of diagnosis (33, 34).

Data from the USRDS (2011) (10) shows that diabetes was the primary diagnosis in 44% of new ESKD patients (figure 1. 4) and 39% to 53% of prevalent patients in 2009. The incidence rate of ESKD caused by diabetes remains high in the United States, reaching 647 pmp in 2009.

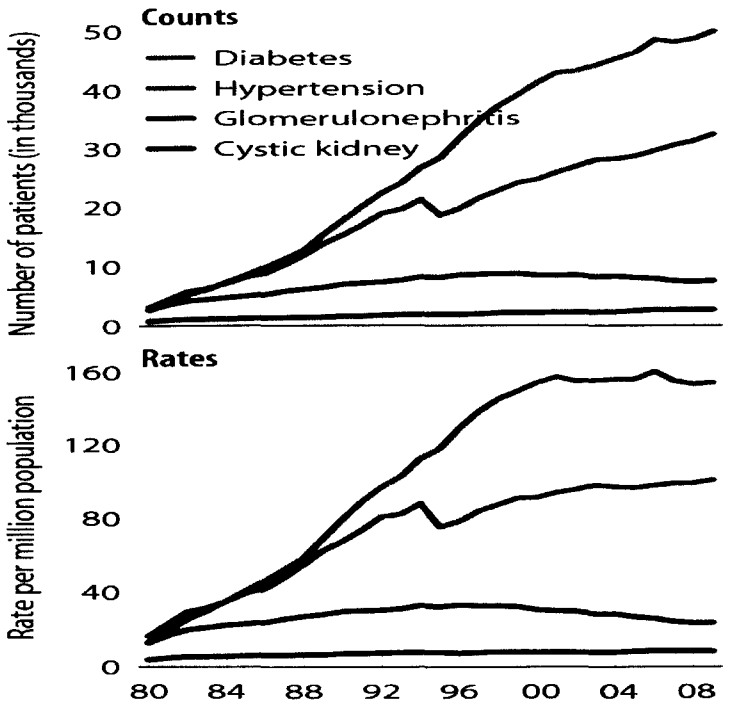

Figure 1. 4: Incident counts and adjusted rates of ESKD, by primary diagnosis, United States Renal Data System (2011)

International figures reported by the USRDS (2011) (10), showed that diabetes was the primary cause of ESKD in 58–60% of new patients in Malaysia, Morelos (Mexico) and Jalisco (Mexico). It also showed that Thailand, New Zealand, Hong Kong, the Republic of Korea, Japan, Taiwan and the Philippines all have rates of ESKD incidence due to diabetes of greater than 40%. In contrast the report showed that incidence of ESKD due to diabetes was below 20% in Iceland, Romania, Ukraine, Montenegro, Russia, Estonia and Latvia. The ERA-EDTA Registry (11) showed a lower frequency of diabetes as the primary disease causing ESKD (20% or less) in Norway, Iceland, Russia, the Netherlands and Romania.

The UK Renal Registry report (12) showed that diabetic nephropathy was the most common specific renal diagnosis causing ESKD in both the under and over 65 year age groups, accounting for 25% of all incident diagnoses. The Australia and New Zealand Dialysis and Transplant Registry (13) showed that in Australia, diabetic nephropathy was the primary cause for ESKD in 33% of new patients, while in New Zealand, diabetic nephropathy was the primary disease in 47%. Several reports from Middle East countries including Syria, Jordan,

Lebanon, Turkey and Iran showed that diabetes was the most frequent cause of ESKD in these countries (20-40%) (20, 21, 24, 35, 36).

Other causes of ESKD include hypertension, glomerulonephritis and interstitial nephritis. Numerous population- based studies showed that hypertension increases the risk of ESKD (29, 37-39). Raised systolic blood pressure was an independent risk factor for development of renal impairment among patients with type II diabetes (40). Furthermore, several studies have found a close association between the level of blood pressure and the magnitude of increased risk such that even modest elevations in blood pressure, are associated with increased risk of ESKD (29, 37, 41). Hypertension is projected to increase sharply over the next few decades, particularly in developing nations (42). Data from the USRDS (2011) (10) showed that hypertension was the primary diagnosis in 28% of new ESKD patients and the rate of ESKD due to hypertension has grown 8.7% from 2000- 2009, to 101 pmp. The incidence of glomerulonephritis has remained relatively stable in many countries. However, the contribution of glomerulonephritis to all causes of ESKD has declined due to increase in other causes such as diabetes and hypertension. Glomerulonephritis as a primary diagnosis has fallen to 23.8% in the United States (10). In the UK, glomerulonephritis accounted for 11.5% of all incident diagnoses while hypertension was the primary diagnosis in 6.9%. In Australia, glomerulonephritis caused 24% of cases and hypertension was the primary disease in 14% (13). Higher proportions of glomerulonephritis were reported from China (35%), Kuwait (35%) (43, 44), Costa Rica (30%) (45) and Yemen (25%) (46) whereas lower proportions were observed in Qatar (13%) (16), Sri-lanka (12%) (47) and Pakistan (10%) (48). Accurate diagnosis of glomerulonephritis requires clinicians with competence to perform a renal biopsy as well as pathology services for processing of the specimens and adequately trained pathologists. These resources remain deficient in many countries and therefore many cases of glomerulonephritis are probably not detected.

Congenital and hereditary kidney diseases such as autosomal dominant polycystic kidney disease, Alport's disease, Fabry's disease and congenital nephrotic syndrome may cause ESKD at any age. The proportion of ESKD caused by congenital and hereditary kidney diseases is relatively small but complex genetic factors likely increase the risk of ESKD in a much larger proportion of populations. Among 25,883 incident ESKD patients, 22.8% reported a family

history of ESKD (49) and screening of the relatives of ESKD patients revealed evidence of CKD in 49.3% (50). The impact of ESKD caused by congenital and hereditary kidney diseases is more prominent in communities with high rates of consanguinity such as Middle East countries (51, 52). Furthermore, populations with a high rate of consanguinity have an increased prevalence of adult diseases that are associated with renal insufficiency, such as hypertension, metabolic syndrome and diabetes (51, 53).

Other factors that may also cause ESKD include urinary tract disorders, chronic pyelonephritis and autoimmune diseases such as lupus nephritis. Obesity may directly cause glomerulopathy or provoke glomerular hypertension and hyperfiltration that may contribute to progression to ESKD (54-56).

Despite advances in diagnostic technologies that have facilitated accurate diagnosis of the cause of ESKD in the majority of patients, the aetiology of ESKD remains uncertain in a substantial proportion of patients, even in developed countries with adequate diagnostic facilities. This is in part due to the fact that CKD still goes undetected in many people until it is advanced, making diagnosis more difficult. In developing countries, lack of diagnostic facilities is an important contributory factor.

1.4. Management of patients with end-stage kidney disease

In advanced CKD the rate of deterioration of patients' condition and tolerance to reduced GFR show substantial variation. The optimal timing of dialysis initiation remains uncertain but there is general consensus that the onset of serious symptoms and complications of uraemia including hyperkalaemia, metabolic acidosis, anorexia, nausea, puritis, malaise and fluid overload is a firm indication to commence dialysis (1).

Detecting patients at early stages of CKD and providing proper management slows the progression of the disease and allows a chance for patients and families to be informed about RRT choices. It also creates the opportunity for pre-emptive kidney transplant. Early diagnosis increases the compliance of patients, builds up confidence between patients and health care providers, assists patients and families in coping with the psychological impact of the disease

and maximises chances for rehabilitation (57, 58). Furthermore, if management with dialysis is the agreed plan, there will be sufficient time to create suitable vascular access which improves outcomes on dialysis (59, 60). Conversely, late referral and an unplanned start to dialysis are associated with increased morbidity (61) and reduction in patient survival that persists for at least the first three years (62). Figure 1. 5, demonstrates the relationship between late referral and dialysis survival such that patients referred less than 12 months before dialysis initiation had a significantly increased risk of death (62).

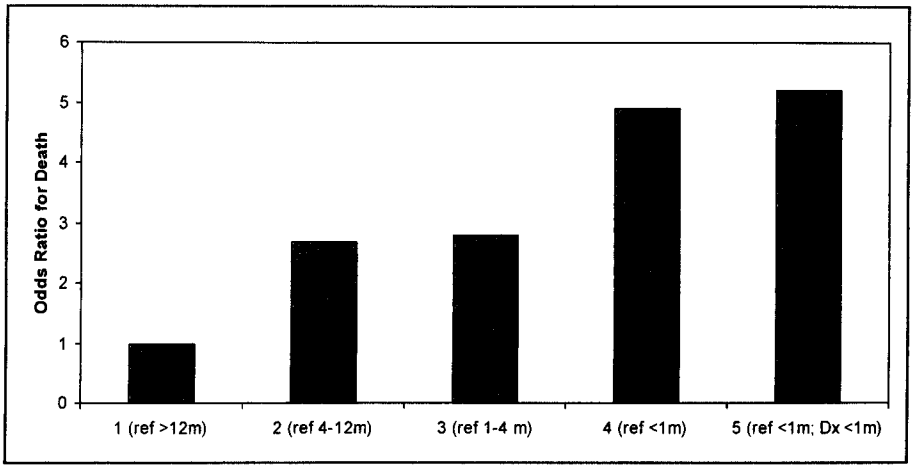

Figure 1. 5: Relation between time of referral before dialysis initiation and subsequent risk of death (Kessler et al. AJKD, 2003)

All clinical guidelines now advocate identifying people at risk of ESKD at an early stage and timely referral to nephrology care to achieve benefits of a planned start. Early referral to a nephrologist, despite being seemingly feasible, is often not achieved. Reports from many countries show that considerable proportions of patients present at late stage and need urgent commencement of dialysis. The USRDS (2011) report (10) showed that more than 43% of ESKD patients starting therapy in 2009 had not seen a nephrologist prior to initiation. Similarly, The Australia and New Zealand Dialysis and Transplant Registry (13) showed that, during 2009, 21% of all new patients in Australia and 17% of new patients in New Zealand were referred to nephrology care in less than three months before first treatment.

Psychosocial support is important for patients, because dialysis makes them socially and emotionally vulnerable (63, 64). It often results in a loss of freedom, dependence on caregivers,

disruption of family life and reduced or loss of financial income. It also interrupts work, school and leisure activities, creates anger, frustration and tension and alters body image because of reduced physical energy (65, 66). Moreover, it causes loss or change in sexual function (67, 68) and changes the body's appearance due to access surgery, dialysis catheter placement, needle marks, bone disease, or other physical deterioration (69-71). Furthermore, dialysis only partially replicates the removal of fluid and uraemic toxins by the kidneys and does not replace any of its hormonal functions. Patients are given other treatments to correct the endocrine deficiencies.

1.5. Renal Replacement Therapy

The main types of RRT are dialysis and renal transplantation. Dialysis is a process in which an artificial kidney or the patient's own peritoneal membrane is used to remove waste metabolites and maintain homeostasis. Kidney transplantation is the gold standard treatment for ESKD where a new kidney replaces the function of failing kidneys, but a shortage of both live and cadaveric donated organs leaves many people with kidney failure obligated to undergo lifelong dialysis. The two dialysis techniques currently available are HD and PD.

1.5.1. Haemodialysis

HD is performed by circulating blood through a disposable dialyzer. This is composed of hollow fibres of a selectively permeable material, giving a large total surface area (1–2 m^2). Dialysate is produced by the combination of concentrate with ultrapure water (microbiologically pure, low endotoxin concentration and depleted in minerals). The dialysis fluid flows around the hollow fibres in the opposite direction to blood. It contains a low concentration of factors to be removed and a higher concentration of bicarbonate, allowing diffusion into the blood and correction of acidosis. Removal of accumulated fluid is achieved by applying a pressure gradient across the dialysis membrane, resulting in controlled ultrafiltration. Figure 1. 6, illustrates a HD machine.

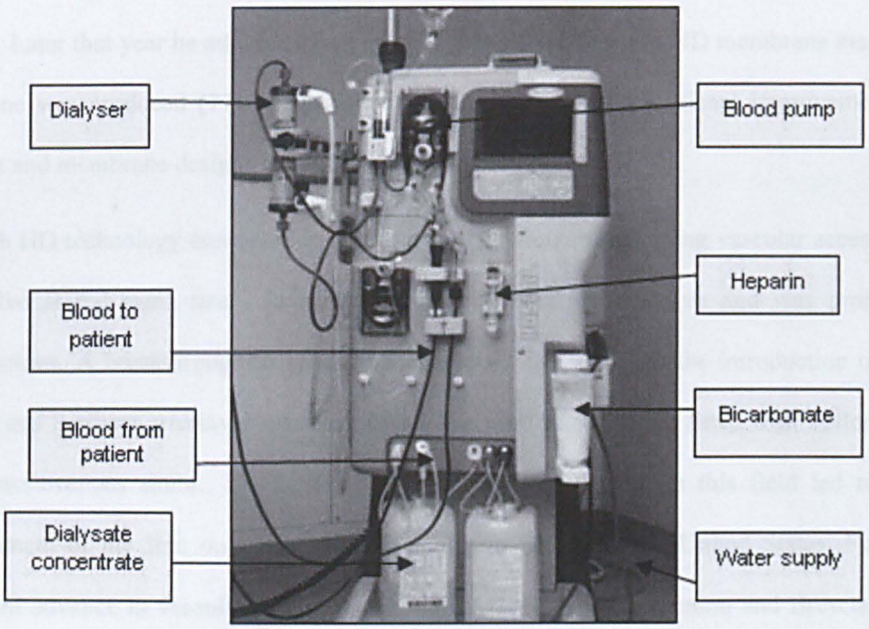

Figure 1. 6: A haemodialysis machine

Conventionally, heparin is used to prevent clotting. HD treatment is performed three times a week, for 3–5 h per session. This results in adequate control of biochemistry (though not normalized), fluid overload, acidosis and uraemic symptoms in most patients.

1.5.1.1. Development of haemodialysis

The enormous advances in medical technology during the past century laid the foundation for the development of dialysis to replace kidney function. The basic theory of dialysis was first described by Thomas Graham in 1854, a chemist at Glasgow University (72). He described the principles of the semi-permeable membrane and gave the name 'dialysis' to refer to the process of selective diffusion (72, 73). Graham realized that, for successful treatment of renal failure, toxins, which accumulate in renal failure, would have to be removed. It would be necessary to understand the production rate of these toxins and the rate at which they can cross the membrane (73). The main cornerstone in HD was laid by Abel, Rowntree and Turner in 1914 when they devised an apparatus for blood dialysis and tested the first efficient dialysis system on animals at Johns Hopkins University School of Medicine (74). The first human HD was performed in a uremic patient by Haas in 1924 at the University of Giessen in Germany (75,

76). He used a tubular device made of collodion and cannulated the radial and carotid arteries. Later that year he added a blood pump. In 1937, the first flat HD membrane made of cellophane was produced (77). This invention was followed by significant improvement in dialysers and membrane designs in 1940's by Kolff (78).

Although HD technology continued to develop, the technique of obtaining vascular access did not evolve at the same rate. Repeated cannulation was not effective and was prone to complications. A breakthrough in vascular access came in 1960 with the introduction of the Quinton and Scribner arteriovenous shunt (79). This used silastic tubes fitted with Teflon tips as an arteriovenous shunt. Dr. Scribner's work and improvement in this field led to the establishment of the first outpatient dialysis centre in Seattle in the United States. Further significant advance in vascular access occurred in the 1960's when Cimino and Brescia first described their native arteriovenous fistula (AVF) for chronic vascular access (80).

Further technological developments led to important improvements in management of blood leaks in the dialysers and lines and the bacterial contamination of the dialysis fluid. Also, production of a commercially viable dialysis solution that contained bicarbonate as a buffer led to reduced hypotension, headaches and hypoxia caused by acetate diaysate (81).

1.5.1.2. Vascular access

Long-term treatment of ESKD with HD is critically dependent on the establishment and maintenance of adequate vascular access. The AVF is regarded as the optimal vascular access in HD patients due to the better patency rates, ability to withstand repetitive needle puncture and association with low patient morbidity and mortality (82-84). An AVF is established by surgical anastamosis of an artery to a vein, forming a high flow, low resistance system. Over a period of 2-3 months the vein enlarges, allowing successful, repetitive venepuncture for HD. Forearm AVF are preferred because of accessibility and less ischemia risks of distal limb in comparison with proximal fistulas (85-87). Patient survival is better when an AVF is used for the first HD treatment compared to starting HD with a catheter and then subsequently using an AVF (84, 88-90). Gender differences in site and patency rates of definitive vascular access have been reported by numerous studies and many have observed that females are less likely

than males to have their permanent vascular access placed in the forearm because they have smaller calibre vessels (91, 92).

Other vascular access options include arteriovenous grafts (AVG), central venous catheters (CVC) and tunnelled catheters. Grafts are used as an alternative when AVF formation is not technically possible. Instead, connection between an artery and a vein is created using a piece of synthetic material such as polytetrafluoroethylene or biological material (biograft). Temporary CVC are used when no alternative access is available. Tunnelled CVCs are designed to be used for longer periods when permanent vascular access cannot be achieved or is delayed. Several clinical guidelines and strategic plans addressing vascular access have been developed to improve practice in this field. The updated NKF/KDOQI goal for vascular access use strongly recommended AVF as the vascular access of first choice for HD and AVGs as second line; the use of CVCs to be kept to a minimum (93).

1.5.1.3. Advances in haemodialysis technology

To improve the quality of care for dialysis patients and increase the efficiency of the process, various modifications of the HD technique have been developed. Advances include dialyzer design and high flux membranes, volumetric control and monitoring systems that provide online clearances. Additionally, convective clearance modalities such as hemofiltration and hemodiafiltration confer benefit in terms of stability on dialysis and greater clearance of some of the larger uraemic toxins (94). Other technical areas include dialysate buffer, electrolyte concentration and temperature, prescription monitoring, volume-ultrafiltration control, information system interface, arteriovenous access monitoring, water treatment and nocturnal dialysis. Currently researchers are developing a wearable device to perform HD (95).

There is also a resurgence of interest in home HD, with improvements in water-treatment and machine portability and the increasing realization that with daily overnight dialysis, or daily short-session dialysis, there can be significant improvements in anaemia, calcium-phosphate balance, acidosis, nutrition, blood pressure, lipid profiles and left ventricular hypertrophy compared to 'standard' thrice weekly four-hour sessions (96-99). It is likely that the escalating numbers of patients on treatment with increasing co-morbidity load will require continued

refinement of dialysis techniques, whilst not replacing the need for early identification of CKD and assiduous mental and physical preparation in the pre- dialysis period.

1.5.2. Peritoneal dialysis

This technique involves using the peritoneum as a dialysis membrane. Pre-packaged fluid is instilled into the peritoneal space via a permanent silicone Tenckhoff catheter. It is allowed to dwell for a period of time (4 hours for continuous ambulatory PD). Waste products to be removed diffuse from the blood into the fluid. Again, the dialysis fluid contains factors that do not need to be removed at similar concentrations to normal plasma (calcium, magnesium and sodium). Acidosis is corrected by the diffusion of buffer from the fluid into the blood and ultrafiltration occurs down an osmotic gradient. This is produced by the fluid having a higher osmolality than plasma (due to a high concentration of glucose or glucose polymer within the dialysis fluid). Rapid drainage relies on good tube placement and function. The most common cause of failure is constipation with tube displacement, or inspissation of omental fat into the catheter's multiple distal perforations. PD patients characteristically are prescribed aperients to promote two soft bowel motions per day. The main limitations of PD relate to the development of peritonitis, resulting either from an infection of the exit site or contamination due to poor technique. There are a number of variants of the PD method. CAPD involves 3–5 exchanges of fluid per day, every day. The patient performs these manually, with the bag being disconnected between each exchange. In some patients, PD treatment is performed at night using automated PD either because more intensive dialysis is needed or for social reasons (100).

1.5.3. Choice of dialysis modality

Although there may be overriding medical or social imperatives in some cases, the choice between PD and HD (either unit or home based) should generally be free and not constrained by either clinicians prejudice or resource issues. Sufficient time and information must be provided to allow patients and families to make a choice. Poor or compelled choice will result in a higher chance of treatment failure and poorer long-term outcomes.

1.5.4. Provision of dialysis

Dialysis is a life- saving measure for patients with ESKD. Currently, over 2 million people require RRT to sustain life worldwide (5, 101, 102) but the number in need of dialysis is increasing globally. The incidence and prevalence of patients with ESKD in the United States expected to increase by 44% and 85%, respectively, from 2000 to 2015 (103). In many developed countries the high cost of dialysis is partially or completely covered by government funds. However, over 100 countries in the developing world fail to provide an open access to dialysis therapy due to economic constraints (6, 7). Actually, treatment of ESKD is a low priority for public hospitals in many poor countries resulting in the estimated death of over 1 million people annually from untreated kidney failure (6, 7). For instance, in India and Pakistan, less than 10% of all patients with ESKD receive any kind of RRT (104, 105).

As the need for dialysis services is escalating, many dialysis units run to full capacity and the need to expand the services is a serious challenge facing health care authorities. The annual growth of dialysis programmes ranged between 6% and 12% over the past two decades and is continuing to grow, particularly in developing countries (106). Capacity expansion requires new dialysis facilities but also training and recruitment of adequate staff. Capacity planning requires accurate knowledge of current and predicted number of patients. Other important services directly related to dialysis provision include pharmacy, laboratory services, technical support to maintain and repair dialysis machines, monitoring of water quality and surgical services for creation of permanent vascular access or insertion of PD catheters.

Provision of dialysis in a country may be improved by the establishment of a Renal Registry to compile national data, audit service capacity and quality and provide feedback to individual units.

In the last few years, growing interest and attention have been paid to the quality of health care services generally and to the delivery of dialysis therapy in particular. The development and implementation of clinical practice guidelines is one way to promote best practice and improve quality. Comprehensive care offered by a multidisciplinary team (that includes; nephrologists, dialysis nurses, renal technicians, dieticians, pharmacists, psychiatrists, surgeons, social workers, counsellors and occupational therapists) is needed to achieve favourable outcomes.

Of concern is the observation that persons with ESKD are reported to have a lower quality of life than persons with other chronic illnesses (107) and that quality of life is correlated with hospitalisation and death in persons with ESKD (108). A low quality of life associated with dialysis may be related to physical complications common in ESKD, such as fatigue, joint pain and anorexia. Low quality of life may also be due to general health perception, socioeconomic status, marital problems, time spent on HD, comorbidities associated with renal failure, side effects of multiple invasive procedures, adverse reactions to drug therapies and uncertainty about the future (109). A unique stressor in the population with ESKD that is not shared by others with different chronic diseases is the need for vascular access. Many patients worry about the integrity of the vascular access, fear it being damaged and view it as an embarrassing disfigurement (109).

1.5.5. Monitoring of patients receiving dialysis

The aim of long-term dialysis therapy is to replicate as far as possible the normal function of the kidney(s). Patients are monitored, usually monthly, for a wide range of indices relating to solute clearance, mineral metabolism, volume status, nutrition and anaemia. Clearance of urea is measured by blood sampling before and after HD, or with a combination of blood samples and samples of waste fluid in PD. Failure to reach certain thresholds is associated with increasing symptoms and increased mortality. Other laboratory investigations indicated to monitor dialysis patients include haemoglobin concentration and haematocrit as well as serum calcium, phosphorus, albumin and parathyroid hormone.

1.5.6. Adverse effects of dialysis

Long-term dialysis treatment impacts on multiple body systems since the kidneys are responsible for a wide variety of physiologic processes including clearance of metabolic waste products, maintain acid-base balance, regulation of sodium and potassium excretion, regulation of extracellular fluid volume and blood pressure as well as hormone production. The extent of

complications experienced by patients on dialysis may be enhanced by interaction between ESKD and coexisting conditions like diabetes, obesity and aging.

1.5.6.1. Uraemia

Patients on long term dialysis suffer from several complications attributed to the effect of uraemia which cannot be completely reversed because of the short and intermittent nature of dialysis. Uraemia causes fatigue, loss of concentration, sleep disturbances, restless legs, peripheral neuropathy, platelet dysfunction, anorexia, nausea, itching and cramps. Nevertheless, the effect of uraemia may be minimised by optimal delivery of an adequate dose of dialysis.

1.5.6.2. Cardiovascular system

Cardiovascular disease is the dominant cause of death in patients on dialysis. Several structural and functional peripheral vascular and cardiac abnormalities contribute to cardiovascular disease including left ventricular hypertrophy, reduced coronary blood flow, impaired microcirculation, reduced peripheral arterial compliance, arterial calcification and myocardial ischemia (110). The complex interaction between retained metabolites, inflammation, oxidative stress, malnutrition and the impact of recurrent volume overload with rapid fluid shifts that occur on dialysis ultimately leads to cardiomyopathy, cardiac failure and death (111, 112).

1.5.6.3. Hormone deficiency

While dialysis partially replaces glomerular filtration, patients on dialysis still suffer from hormone deficiencies including calcitriol and erythropoietin. Hyperphosphataemia and low calcitriol levels provoke secondary hyperparathyroidism. In addition to effects on bone metabolism, the elevated calcium- phosphorus product associated with secondary hyperparathyroidism may cause arterial calcification that contributes to arterial stiffness and cardiovascular disease.

Erythropoietin is the other hormone that is uniquely synthesised by the kidneys. It is responsible for activation of bone marrow erythroid precursors. However, the anaemia

commonly occurs in ESKD is usually caused by a combination of factors that include erythropoietin hormone deficiency, functional iron insufficiency and chronic inflammation (113). Other factors include, shortened red blood cell survival, blood loss related to HD and uremic inhibitors of erythrocyte production.

1.5.6.4. Nutritional disturbances

Both ESKD and dialysis have effects on the nutritional status of patients (114). Malnutrition commonly arises from inadequate protein or calorie intake, increased energy expenditure, dialytic nutrient loss, metabolic acidosis, dialysis induced catabolism, hormonal alterations and infection. Albumin may be a marker of nutritional status but is also reduced by acute illness.

1.5.6.5. Bacterial infection

Bacteraemia is a common problem in dialysis patients (115). Sepsis ranks second behind cardiovascular disease as cause of death in patients treated with long-term dialysis. Infections rates continue to be high despite application of infection- control programmes in many dialysis facilities. Many of these infections are dialysis access related but other infections are also frequent. They include respiratory tract infections, endocarditis, skin and soft tissue infections and urinary tract infections. Vascular access related infections are commonly caused by *Staphylococcus aureus*. Elderly and diabetic patients as well as those using catheters for vascular access are more vulnerable to infections. Uraemia causes reduced leukocyte chemotaxis and phagocytosis, increasing susceptibility to infection (116). The treatment of infections may be further complicated by increased antibiotic resistance in dialysis patients due to repeated exposure to antibiotics.

1.5.6.6. Viral hepatitis

Patients undergoing HD have excess risk for acquiring blood bourne virus infections. The prevalence of hepatitis B and hepatitis C virus (HBV and HCV) infections in dialysis- treated patients is commonly higher than the general population (117, 118). HBV and/or HCV infections in dialysis patients increase morbidity and mortality risks due to liver disease and reduced immunity. The prevalence and incidence of HBV and HCV infections among dialysis patients varies widely between countries and also within the same country and it correlates

with the prevalence in the general population. Global data indicate that the prevalence of HBV and HCV infection is high in the populations of Africa and the Middle-East regions (119-121).

The overall prevalence of both infections in maintenance dialysis patients is decreasing in many countries. The prevalence of HBV infection in dialysis patients in Western Europe and the United States ranges between 0% and 7% (122) . Reports from Hong Kong and Brazil showed higher prevalence of approximately 10% (123, 124). Data from Saudi Arabia showed a prevalence rate of 4.6% (19) and from Jordan of 5.9% (125). A low rate of 1.6% was reported in Japan. The prevalence of HCV sero-positivity, on the other hand, is generally higher than HBV in dialysis populations though it differs widely between countries. Previous epidemiological studies have shown that the prevalence of HCV sero-positivity among patients receiving HD varies from as low as 6.1% in Germany (126) to as high as 76% in Casablanca (127). Reports showed that the prevalence of HCV sero-positivity in HD patients was 50% in Saudi Arabia (128), 42% in Tunisia (129), 20.2% in Turkey (130) and 21% in Jordan (20).

Incidence of hepatitis B surface antigen (HBsAg) seroconversion is declining in many dialysis facilities due to adherence to strict isolation of seropositive patients and administration of HBV vaccine to seronegative patients. The incidence rate in majority of facilities (78.1%) in Western Europe and the United States included in the Dialysis Outcome and Practice Patterns Study (DOPPS) was 0 per 100 patient-years (122). Rates of annual HBV seroconversion are higher in developing countries. The incidence of HCV sero-conversion in Saudi HD patients was reported to be 7-9% per year (19) while in Jordan it was 2.6% (20).

Multiple factors contribute to the increased risk of HBV and HCV infections among dialysis patients. Observational studies carried out in various centres worldwide have shown that the number of blood units transfused (126, 131), the duration of HD (131-134), a history of previous renal transplant (134-136), presence of HBV and/or HCV positive patients in the same facility and non-isolation of seropositive patients are associated with an increased risk of infection (137, 138). Historically, blood transfusion was the main factor implicated in transmission of HCV infections in dialysis patients. Despite increased safety of blood products and reducing the need for blood transfusion by the use of recombinant erythropoietin hormone, transmission by this route seems to be still occurring in some countries, probably because of

delayed appearance of serological markers in some blood donors or poor quality of laboratory testing (139).

Additionally, HD patients are predisposed to nosocomial transmission of HBV and HCV infections from seropositive patients because each treatment is associated with a small amount of blood loss from needling sites and discarded lines (140, 141). The most effective measure for preventing this is to isolate seropositive patients to dialysis stations in separate rooms but strict application of infection control procedures including safe disposal of contaminated medical waste are also important. Patient to patient transmission is confirmed by demonstrating similarity of subtypes and genotypes in patients receiving treatment in the same HD centre, sharing the same room or sharing the same HD machine (142).

1.5.6.7. Vascular Access related complications

Creating and maintaining a successful permanent vascular access is a major challenge for HD staff even in advanced and well organized health care systems because of a high incidence of dysfunction and failure. The need for secondary intervention to maintain vascular access is common. Furthermore, failure of new AVF to mature is observed in at least one third of cases (143). Data from DOPPS III (2005–2007) from 11 countries showed wide variation in vascular access patterns among countries with a highest rate of AVF use (91%) in Japan and the lowest rate (47%) in the United States. Vascular access related complications account for 16–25% of hospital admissions in dialysis patients and depending on the type of vascular access in use, this correlated with overall and cause-specific mortality (84). Similarly, the USRDS (2011) reported that HD access failure was the most frequent cause of hospitalisation.

Late referral and lack of predialysis nephrology care are the main reasons for high rates of CVC use at dialysis initiation. DOPPS II reported that 23–73% of patients new to ESKD used a catheter for the initiation of HD (144). Barriers to AVF placement are patient preference, unfavourable anatomy, lack of surgical expertise and late referral of patients to nephrologists and vascular surgeons (145-147). Diabetes has also been identified as a risk factor for reduced utilisation of AVFs (91, 148, 149).

Thrombosis is a leading cause of vascular access failure. Early thrombosis is associated with poor outcome as salvage is not usually attempted due to low success rates. Late thrombosis is

usually related to an underlying stenosis of the fistula and a variety of monitoring techniques have been developed to detect stenosis before thrombosis occurs. Vascular access related infection is a serious complication which often results in hospitalisation. Infections account for approximately 15% of all deaths in this patient population and for about one-fifth of admissions. Infections are usually associated with CVCs. Most studies showed that the risk of vascular access related bacteraemia is greatest with temporary CVCs and decreases progressively with tunnelled CVCs, AVGs and AVFs (150-153). Damage and weakening of the vessel wall following repeated cannulation can also lead to excessive dilatation and aneurysm formation.

1.6. Survival of maintenance dialysis patients

Despite optimal treatment, patients on maintenance dialysis have substantially reduced survival rates when compared to the general population. Patient survival is therefore the most fundamental outcome measure for patients receiving dialysis. Survival trends are best described by longitudinal observational studies such as those obtained from renal registry data. In the short term, annual mortality rate is recognised as a useful tool to assess and compare dialysis outcomes between different providers. A considerable body of research aimed at determining the factors associated with excess risk of death in dialysis patients has led to multiple reforms in the clinical practice guidelines. Mortality rates have declined modestly in the United States, Europe and Japan over the last two decades after modifiable risk factors for reduced survival were targeted (10, 154).

1.6.1. Factors associated with increased mortality in dialysis patients

Excess risk of death in patients receiving maintenance dialysis is related to multiple interacting factors that include;

- Factors related to characteristics of dialysis patients such as demographic and socio-economic status (155), timing and quality of predialysis nephrology care (156), pattern of initiation of dialysis and presence and type of comorbidity (157). Most accompanying diseases adversely affect survival. Patients with CKD have a higher prevalence and incidence of cardiovascular disease such as ischemic heart diseases and heart failure (158, 159). Other patient factors associated with elevated mortality rate includes; diabetes, hypertension, hypotension, smoking, dyslipidaemia, inactive life style, arteriosclerosis, malnutrition abnormal bone and mineral metabolism and male gender (160-164).

- Factors related to the delivery of dialysis such as the mode of dialysis, location of dialysis facility, presence of trained staff, availability of resources, technical support, water quality and infection control polices (165-168). In addition, quality of services in terms of number of sessions per week, delivered kt/v and monitoring of biochemical and nutritional indicators as well as social and psychological support (169-172).

Mortality rates are high in patients receiving maintenance dialysis. The adjusted rates of all-cause mortality are 6.5-7.4 times greater for dialysis patients than for individuals in the general population (10). USRDS (2011) data showed that only 50% of dialysis patients were alive three years after the start of ESKD therapy (10). At the time of initiation of dialysis, the expected life span ranged from approximately 8 years for patients aged 40-44 years to approximately 4.5 years for those 60-64 years of age (10). The risk of death increased with age and was higher in older men than women (10). The adjusted all- cause mortality among prevalent patients (2009) for the age group 45-64 years was 15.4% and for those who were 65 years or more was 31.3% (10). In a recently published analysis of the ERA-EDTA Registry, the mortality rate in incident dialysis patients was 19.2 per 100 person-years, while it was only 12.05 per 100 patient years in the general population (173). In Japan, the annual death rate has decreased over several years, recently to less than 10% (174).

1.6.2. Causes of death in dialysis patients

Cardiovascular disease is the most common cause of death in dialysis patients and includes ischemic heart disease, arrhythmias, congestive heart failure and cardiomyopathy. The HEMO Study identified ischemic heart disease to be a major cause of cardiac deaths (61.5%) (175). Vascular diseases such as arteriosclerosis, arterial calcification and aortic aneurysm are also important factors associated with mortality. The aetiology of cardiovascular diseases in dialysis patient is not fully understood. In addition to a high prevalence of traditional cardiovascular risk factors a variety of dialysis related factors probably play a role including the state of uraemia, hypervolaemia, hypertension, metabolic acidosis, hyperparathyroidism, B-2-microglobulinaemia and elevated endotoxins in patients. Stroke is common in dialysis patients and it is associated with poor outcome. Results of the HEMO Study showed that cerebrovascular death in maintenance HD patients was associated with diabetes, lower albumin level, greater heamatocrit and lower body mass index (176).

The uraemic state also induces immunosuppression which may contribute to excess infection rates in these patients. Infection is the cause of death in approximately 15% to 30% of all dialysis patients (177). Septicaemia and pneumonia are the most common infections associated with death. The presence of a CVC is the most important cause for septicaemia leading to death in HD patients. Low physical activity levels, muscle wasting, weakness and frailty are also associated with an increased risk of death in dialysis patients (178).

1.7. Renal Registries and research in dialysis

1.7.1. Renal registries

In many countries a renal registry has been established to collect and analyse data regarding multiple aspects of kidney disease and its treatment. Data from dialysis and transplantation programmes are collected at regular intervals and analysed to yield national data. The aim of a renal registry is to provide an ongoing audit of national data to inform efforts to improve treatment outcomes and to facilitate research. Registries are useful in characterising the ESKD

population, describing the incidence and prevalence of ESKD as well as trends in mortality and morbidity. They act as a good tool to investigate relationships between patient demographics, treatment modalities, clinical management and morbidity (179). Renal registries provide powerful epidemiology data because they have access to nationally comprehensive patient-level data and track outcomes. Data provided by renal registries are used by health care authorities in planning the provision of dialysis services and to predict future expansion. Moreover, renal registry data should play an important role in the development of clinical practice guidelines as they represent an important source of evidence to inform best practice. Registry information also helps in auditing dialysis services by studying the variation in key indicators. A yearly report is usually published to help health care providers assess their performance and facilitate improvement programmes. Accuracy of information pooled from the peripheral centres as well as standardising the statistical methodology to allow international comparisons are important challenges for renal registries. Absence of a renal registry in some countries limits data to small observational series or reports, making it difficult to draw conclusions that could be applied nationally.

1.7.2. Dialysis related research

As a relatively new form of therapy associated with multiple adverse effects, dialysis has attracted the attention of researchers seeking to evaluate outcomes and develop methods for improving them. Results from renal registry reports as well as other research have highlighted major differences in the quantity and quality of dialysis provision across the world. The variations are partially explained by disparity in demography of different regions, ethnicity, social disparity, economic status and prevalence of diabetes and hypertension in communities. The provision of dialysis is also strongly related to the wealth and overall development of a society.

Over the past 10 years, monitoring and improvement of dialysis practice has led to the development of several sets of clinical practice guidelines, such as those of the NKF/KDOQI, to help practitioners provide the best possible care.

In addition to renal registries, a considerable body of research has evaluated clinical practice in dialysis provision and its relation to outcomes. Important projects in this regard include:

1.7.2.1. Dialysis Outcome and Practice Patterns Study (DOPPS) (http://www.dopps.org/)

DOPPS is a prospective cohort study of dialysis practice based on the collection of observational longitudinal data on patients from a representative and random sample of units in 12 countries (Australia, Belgium, Canada, France, Germany, Japan, Italy, New Zealand, Spain, Sweden, the United Kingdom and the United States). Data collection for the study has been on-going since 1996 and has yielded detailed data on more than 38,000 patients in over 900 dialysis facilities. DOPPS investigations focus on determining which dialysis practices are associated with the best patient outcomes, with the primary goal of improving patient longevity, quality of life and other outcomes.

1.7.2.2. The International Study of Health Care Organisation and Financing (ISHCOF)

ISHCOF examines how the treatment of renal failure is paid for around the world and how the services are organised and delivered to the patients (180-182). The ISHCOF is a sub-study of DOPPS.

1.7.2.3. Dialysis practice research

Researchers in different countries have also studied many aspects of ESKD and dialysis (102, 105, 183-185). Major aspects of dialysis practice that have been addressed include:

- General trends in dialysis-treated ESKD such as incidence and prevalence rates, geographical, ethnic, gender and age variations as well as causes of ESKD and dialysis outcomes.
- Indicators of provision of services, in terms of number and distribution of dialysis facilities, bed capacity, number of working days/week and working shifts/ day.

- Availability of a qualified multidisciplinary team measured by the proportion of staff from each specialty to the number of patients treated.
- The complex effect of ESKD and dialysis on patient's health and the effect of coexisting comorbidity.
- Clinical and biochemical monitoring of dialysis patients in terms of adequacy of dialysis dose, control of anaemia, normalisation of bone mineral metabolism and sufficient nutrition.
- Nosocomial transmission of infections in dialysis units and methods to prevent them.
- Technical issues like biological and chemical quality of dialysis water and type of dialysis membrane used.
- Measures to protect the environment through sanitary disposal of the dialysis consumables.

1.8. Libya: Current social, demographic, economic and political factors impacting on healthcare

The overall pattern of ESKD varies considerably according to the social, cultural and economic context of a country. Some important aspects about Libya will be briefly discussed. These aspects mostly apply to the time the study was undertaken, as major changes have occurred due to the internal conflict that began in February 2011.

1.8.1. General features

Libya is a vast country (4th largest country in Africa) with an area of 1,665,000 square kilometres. Its total population reached 5,673,031 persons in the 2006 census (186). Amongst these, 6% were non- Libyan residents. In spite of a low overall population density of three persons per square kilometre, the majority (85%) of the country's population are urban and live in the coastal regions. A map of Libya is shown in figure 1. 6.

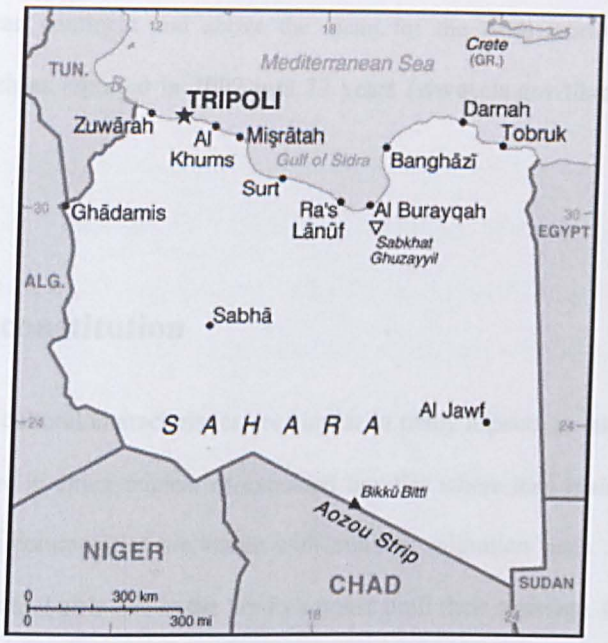

Figure 1. 7: Map of Libya showing that most of the cities are in the coastal region. (http://www.who.int/countryfocus/)

Geographically, it can be divided into a green coast and a wide desert. Approximately 88 % of the population lives in the north, near the Mediterranean coast and in the region of the North West and East Mountains chains. The other 12% live in small towns scattered in the Libyan Sahara around valleys and oases. Perpetual drought means that Libya faces strong constraints in terms of availability of water resources and of food self-sufficiency (187).

Administratively, the country is divided into 22 municipalities. Each municipality is divided into communes, which is the basic people's congress. The total number of Libyan communes is 468. The members of each commune meet periodically to discuss political, economic and social issues.

Libya has massively developed its infrastructure and human resources over the past 50 years. The economy depends primarily upon revenues from the oil sector, which contribute about 95% of export earnings, about one quarter of Gross Domestic Product and 60% of public sector wages. Libya is considered to have one of the highest per capita Gross Domestic Products in Africa. Overall, it is classified as a medium- developed country in the United Nations Development Programme's Human Development Index, where it is ranked 58th out of 178 countries (www.nationmaster.com). Generally, most development indicators are among the

best in the African continent and above the mean for the Arab world. For example, life expectancy at birth as reported in 2007 was 77 years (www.cia.gov/library/publications/the-world-factbook/).

1.8.2. Social constitution

Libya's social and cultural characteristics are similar in many aspects to other Arab countries. Libyans tend to live in either nuclear or extended families where they maintain strong social relationships. Most communities are stable with minimal migration rates. As a conservative tradition, most boys and girls live in the family's house until their marriage. Chronically ill and disabled persons are looked after by family members. Almost no nursing homes are available in the country and just a few rehabilitation institutions in the main cities.

Several cultural features of the Libyan society probably adversely affect people's health and increase the risk for CKD either directly or indirectly. First, people in this country tend to adopt a sedentary life style (188). Physical activity is very limited especially among women. A population based study was undertaken in the town of Tajoura, in the west of Libya which included 2996 adults showed that only 18% of surveyed people were practicing any form of physical exercise and more than 69% had a body mass index of more than 25 kg/m^2 (188). Physical work including construction, agriculture and industry is carried out mostly by expatriate labour. Private transport (mainly cars and minibuses) is considered socially superior to walking as it expresses wealth. Additional factors that contribute to Libyans' inactive way of life include; the habit of socialization by visiting each other indoors, the hot sunny weather which inhibits walking during day time, the poorly developed pedestrian and cycling infrastructure, the shortage of public green areas in most cities and the lack of well-structured health education programs.

Libya has an average of six deaths per day due to road traffic accidents and according to the figures for 2009 alone, over 14,000 injuries from road traffic accidents, almost half of which were severe. Road fatalities are 31.5 per 100,000 population in comparison with 6.1 in the UK

(http://www.emro.who.int/). According to World Health Organisation reports, Libya has one of the highest death rates from road traffic accidents in the region.

The second cultural aspect which negatively affects people's health is the Libyan diet (189). It is rich in carbohydrates and fats but poor in fresh vegetables. Meat and poultry are principle ingredients in many local daily dishes (190). This diet is dense in energy and poor in micronutrients (189). Consequently adults especially women are affected by a high prevalence of overweight and obesity. A recent survey showed that 15.5% of 13-15 year-old school children assessed were overweight and 6.1% were obese (186). Deficiency in micronutrients like iron is highly prevalent (191). Reports also showed that about 30% of the adult male Libyan population are regular smokers (186).

Currently, awareness among the public of the risks of this negative life style has substantially increased due to media coverage, but only a minority have actually changed their lifestyles.

1.8.3. Social security system

Libyans benefit from a social security program, which promotes welfare of people in the event of old age, disability, sickness, accidents, occupational diseases, childbirth and unemployment (192). A basic pension is payable to all disabled persons, including all ESKD patients receiving any mode of RRT. The amount depends on the type of previous work, years of experience and the extent of the disability.

1.8.4. Health care system

Since the early 1970's, Libya has attained marked improvements in the health care sector. Expansion was made possible by building hospitals, polyclinics, laboratories, medical schools and other health care infrastructure (186). Training the necessary work force to deliver health care services for the expanding sector was undertaken in parallel with building of facilities (186). Some recent indicators of the health care sector reported in 2007 are shown in Table 1. 2.

Table 1. 2: Indicators of health care sector in Libya (WHO Statistical Information System. (http://www.emro.who.int/emrinfo/index)

Primary health care centres	1424
General Hospitals	21
Central Hospitals	18
Provincial Hospitals	32
Specialized Hospitals	25
Number of doctors/10.000	17
Number of nurses/10.000	50
Number of Hospital beds/10.000	37

Although health care services are available and free for all citizens and residents in Libya, their quality is suboptimal. A state budget is allocated each year to cover the cost of health care delivery. A recent estimation of the total expenditure on health per capita is $298 per year, which is considered medium for countries in the region but low for the developed nations (http://www.emro.who.int/emrinfo/index). The main causes of death reported by national authorities in 2010 were cardiovascular diseases (37%), cancer (13%) and diabetes (5%). Road traffic injuries accounted for 11% of all deaths.

However, Libya's health care system suffered greatly in the 1980's and 1990's because of the United Nation's sanctions and Libya's isolation from other countries (186). Sanctions included medical equipment and technology as well as technical support. Education, training abroad and representation of Libya in scientific organisations was suspended. Many qualified doctors moved outside the country, which resulted in a 'brain drain' and loss of expertise (193). Sanctions markedly affected the young and fragile health care system. After the lifting of sanctions, enormous deficiencies in the health care services were obvious. Health care policy

makers planned for rapid growth to meet the consumer's expectations and to catch up with ever-increasing demand. Lately arguments between the users and staff about the overt deficiency of the Libyan's health care system and its inefficiency had have arisen (194). A decision to reform the health care sector with the explicit aim of improving performance was recently undertaken. It included introducing many organisational changes. An important example is recruiting hundreds of young medical practitioners from different specialties to enrol in a specially tailored family physicians graduate program in order to form the nucleus of family practice in the country. Generally, the rehabilitation of the health care system in Libya was ineffective due to lack of proper organisation, mismanagement, negligence and corruption.

In practice, the Libyan health care system has always been dominated by the idea of treating patients rather than promoting the health of people and preventing them from becoming ill. A large amount of the health care budget is spent in purchasing modern sophisticated technology and expensive medication, which are used mainly at secondary and tertiary care level while most primary health care (PHC) facilities experience shortage of basic equipment and medicine (194). Furthermore, despite the expansion of PHC facilities throughout the country, there is no system to sustain a link between local people and their PHC facilities. People are not directed to register with a PHC facility. Instead, they just walk in to any PHC centre whenever they fall sick and/or are exposed to injury. Staff in the PHC focus primarily on treating urgent problems or referring patients to the secondary care level. Clinics in PHC are staffed principally with inexperienced medical graduates. Many of them lack job satisfaction because of a deprived work environment, lack of education and training programs and low income as compared to their counterparts working in hospitals. Nursing and medical technology staff are local graduates who are inadequately trained resulting in a poor quality of practice.

Collectively, several factors worsen the state of mistrust between people and the health care system. Even in the secondary and tertiary health care levels, Libya still finds itself facing a shortage of specialists in a number of key areas such as family medicine, anaesthesia, nephrology, cardiology and radiology. Despite large numbers of medical students and large amounts of funding for scholarships for doctors to specialize abroad, many choose to make their careers abroad (http://www.who.int/countries/lby/en/). Recently, the General Medical Council confirmed that there are 707 doctors registered in the UK who obtained their primary

medical qualifications in Libya (195). Another negative contributory factor is an inadequate standard of nursing care due to poor quality nursing education and training.

1.8.5. Health records

Medical records are necessary to retain all relevant data about a patient that clinicians need to support clinical decision making at the point of care. Unfortunately, almost no medical records are kept in the PHC facilities. At secondary and tertiary care levels, a traditional paper record is maintained for each patient for saving all clinical and administrative patient information, including laboratory results, pharmacy orders, radiology reports, medical graphs, electrocardiograms and nursing as well as physician notes (196). Records are sent to the medical information department to be kept in the archives shortly after a patient's discharge or death. In many hospitals, however, medical archives are poorly organised and difficult to access. Consequently, capturing longitudinal data is difficult. Recently, a trial of electronic medical records was initiated in a small number of hospitals. Economic constraints on the health care sector make expansion of these trials slow.

ESKD patients are among the patients adversely affected by the medical record system because their significant past medical history and other medical data generated at the time of diagnosis in hospitals are kept locked in hospital archives. Patients are sent to dialysis units with a brief referral report only. In dialysis facilities, a new medical record is provided for each patient. It is mainly concerned with reporting dialysis-related information.

1.8.6. Medical research

Medical publications are indicators of the quality of health care services and medical education in countries (197, 198). Medical education in Libya does not emphasize medical research in undergraduate or postgraduate studies. Moreover, the underdeveloped research environment in many Libyan health care and academic facilities exacerbated by the absence of research funds and incentives hinders health related research and makes it a low priority for medical staff

(199, 200). The annual publication rate for academic staff in peer-reviewed journals is estimated to be around 0.7 publications/100 staff, which is considered among the lowest rates in the middle east region (201).

1.8.7. Diagnosis of ESKD cases and referral for RRT in Libya

The typical mode of presentation with ESKD is for a young or middle-aged person with insignificant past medical history to be rushed to a clinic after the development of uraemic symptoms. Such patients usually present themselves to PHC, general hospitals or private clinics. Once the diagnosis of ESKD had been confirmed by laboratory tests, patients are usually referred urgently to medical/nephrology departments to receive HD through a CVC. Patients and their families experience sudden emotional shock, especially if the case is unprecedented within the family. In many instances, people do not believe the doctor's unexpected diagnosis because they lack trust in the local health care system and seek another opinion either within or outside the country. Several patients travel abroad for consultation and treatment in Tunisia, Egypt, Jordan and further (202). Finally, most patients who survive the initial critical period of illness are established on chronic HD in the nearest dialysis centre. Discussion about other options for RRT and/or vascular access usually starts later on.

The second less dramatic and less common scenario is of a middle aged or old person who has an established renal, urologic or chronic systemic illness that are known to affect kidney function. These patients are usually offered nephrology consultation, follow up and treatment when they were diagnosed as having CKD. They usually take part in decisions about the type and the timing of RRT.

1.8.8. Renal replacement therapy in Libya

All types of RRT are funded by the state. All available services are delivered to citizens and residents free of charge. However, because of their enormous cost, these services are provided exclusively by the public sector.

The first HD service in the country was started in Aljemhoria Hospital in Benghazi city in 1973. This service gradually expanded in numbers of both patients and centres. PD was introduced as a trial in the 1990's but has remained at very low level. Kidney transplantation was introduced into the country as a collaborative project between Poland and Libya in 1988. A renal transplant unit was founded in Alzahra Kidney Centre near Tripoli city. Polish surgeons transplanted 63 kidneys from live related donors during 8 years. Eventually, transplantation activities collapsed, largely due to United Nation's sanctions against Libya and subsequent shortage of the immunosuppressive therapy as well as medical equipment.

In 2004 after sanctions were removed, a new transplantation program was initiated in Tripoli Central Hospital (203). Reports show approximately 45 renal transplants per year (204). However, organ transplantation in Libya depends exclusively on the availability of a suitable living related donor (205). Living donors are not available for many ESKD patients as many possible donors are ineligible due to familial renal disease, diabetes or hypertension. Consequently the gap between patients' needs and the transplantation rate continues to widen. Social pressures prompt many medium and wealthy families to seek kidneys from the poor in other countries. A recent survey showed that about 19% of renal transplants among Libyans were carried out in Libya whereas the majority were transplanted abroad, mostly from living non-related donors (206), a practice which encourages organ trafficking and exploitation. After being transplanted abroad, patients often return to the country with minimal and indistinct medical information leaving the Libyan health care system to stabilize them and provide long term care.

A deceased organ donation program was initiated in the country by launching educational campaigns through the media to familiarize people with the concept and motivate them to sign a donor card. However, cadaveric donation in Libya is still hampered by lack of proper knowledge, religious misconception and other psychological factors (207). All renal transplant activities were suspended at the start of the revolution in February 2011 and remain suspended to date.

1.8.9. Recent conflict in Libya

A political clash started in Libya during February 2011 when protestors took to the streets throughout the nation demanding their human rights from a dictator who had dominated the country for 42 years (208). The regime responded with violent offences against the people and this provoked a war which took 8 months to resolve (209). The impact of the conflict is obvious in all life aspects. The health care sector has been massively affected, with many PHC facilities closed because of damage sustained during the fighting, acute shortage of medicines and supplies and departure of many of the expatriate medical staff (210, 211). During the crises, most local staff, volunteers and many international humanitarian organisations collaborated to manage trauma and war injuries but shortage of services and medications affected chronically ill people and added to the overall mortality (212, 213). However, reports about fatalities due to lack of health services during the fighting are not available. Thus, a detailed post conflict assessment of the health care system is required.

1.8.10. The need for studying the epidemiology of end-stage kidney disease in Libya

With the absence of a renal registry and population based epidemiological surveys in Libya, little information is available regarding the extent of renal failure in this community or the patterns of dialysis practice in different health care facilities. Furthermore, the quality and the outcome of medical care provided for dialysis patients have not been described. This knowledge gap necessitates scientific work to generate local data to inform the planning of future development and help in improving the quality of dialysis delivery as well as its outcomes.

Chapter 2

Objectives

2. Aim and objectives

2. 1. Aim

The aim of this thesis is to assess the epidemiological patterns of ESKD in adult patients and dialysis- treatment quality as well as outcomes.

To achieve this, the following objectives were framed:

2. 2. Objectives

- To assess the provision and quality of maintenance dialysis services in Libya.
- To determine the annual incidence, prevalence and causes of ESKD treated with dialysis in the adult population.
- To investigate the incidence and prevalence of HBV and HCV infection in the HD population of Libya as well as risk factors for infection.
- To determine the patterns of vascular access utilisation in Libya and risk factors associated with failure of permanent vascular access.
- To investigate survival rates, determinants of survival and causes of death in the dialysis population.

Chapter 3

Methods

3. Methods

This chapter describes all methods applied in this thesis. The methods comprise those common to all aspects of the research and others relevant only to specific analyses. The latter will be described in more detail in the relevant results chapters.

3. 1. Study location

The study was performed by a Libyan researcher with support and guidance provided by a supervisors based in a Nephrology Department in the United Kingdom. The study plan and design was developed in the United Kingdom. All data were collected in Libya. Finally, data analysis and writing up were performed in the United Kingdom.

3. 2. Ethical approval

Permission to conduct the study was granted by the Ministry of Health in Libya. Ethical approval for the research was obtained from the Libyan National Committee for Bioethics and Bio-safety. Patients were requested to participate in the study and each gave written informed consent before conducting the interview.

3. 3. Pilot study

A pilot study was undertaken in 5 dialysis units. The dialysis facility questionnaire was tested in four dialysis centres and validated through discussion with the clinical directors of surveyed centres. The dialysis patient questionnaire was tested in a sample of 100 patients (20 from each dialysis facility). Difficulties including poor quality of medical records, variation in patient management systems and the need to recruit a local research team were explored and solutions developed.

3. 4. Study plan

- Collection of contact information for all maintenance dialysis facilities in Libya.
- Face to face interview with the supervisors of 28 of 40 maintenance dialysis facilities in Libya, including one paediatric unit.
- Telephonic interview with the supervisors of the remaining 12 maintenance dialysis facilities.
- Clinical supervisors of the 12 dialysis centres not visited were requested to complete a data collection form about each adult patient receiving maintenance dialysis in the facility including CAPD cases if present. Forms sent by special delivery and collected back after 30 days.
- 28 maintenance dialysis facilities were visited by research team (The paediatric unit was not visited for patient interviews). All available dialysis patients were approached and interview requested to obtain detailed medical and social information.
- Frequent contacts to all maintenance dialysis facilities during 1-year follow-up and repeated visits or phone calls to obtain information about patient's outcome and enrolment of new cases.
- Follow-up study of all patients recruited to initial cross-sectional study after 1 year.

3. 5. Research team

Apart from the principal researcher (the author) and two consultant Nephrologists based in Renal Unit in The United Kingdom (the supervisors), the research team included;

Ten medical graduates from different cities in Libya who chose to make joining this study part of their internship training. They participated in data collection at their local maintenance dialysis facilities.

Three medical researchers were appointed by the Libyan National Authority for Scientific Research. They provided assistance in gathering data from some maintenance dialysis facilities.

3. 6. Study design

- Cross-sectional study of dialysis centres was performed from May to August 2009.
- Cross-sectional study of maintenance dialysis patients was performed from May to August 2009.
- Longitudinal study of maintenance dialysis patients was performed from September 2009 to August 2010.
- Follow-up study of all patients recruited to initial cross-sectional study from August to December 2010

3. 7. Study duration

36 months of which data collection took 20 months.

3. 8. Study data

3. 8. 1. Dialysis facility data

Medical directors of dialysis facilities in Libya were contacted initially by phone, informed about the study and asked to participate by answering the questions either by phone or by face to face interview. The principal researcher (the author) visited 28 dialysis facilities (one of them was serving children only) and interviewed the clinical directors of the remaining 12 facilities by telephone. A structured questionnaire was designed to lead the interview. It included four main groups of questions: dialysis capacity, staffing, methods of assessment of dialysis patients and infection control measures. Each personal interview took around 30

minutes while telephone interviews were generally shorter. Each principal contact was interviewed once. Further telephone calls were made to almost all centres to collect missing data, mostly recent statistics regarding patients and staff. In all dialysis centres visited, the head of the facility invited researchers to view the facility.

3. 8. 2. Dialysis patient data

Brief demographic and clinical information were collected for all dialysis patients in Libya included date of birth, gender, ethnicity, nationality, height, weight, type of dialysis, date of dialysis initiation, primary kidney disease, previous renal transplantation, haemoglobin value and sero-positivity for hepatitis B and/or C virus. Date of birth was recorded if known. Otherwise, the year of birth was used. The same applied for the date of first dialysis. Primary kidney disease was recorded according to the opinion of the treating physician or medical reports when available. For the 28 facilities visited (paediatric only facility was excluded from dialysis patient-related study) data was collected by the research team. For the remaining 12 remote dialysis facilities data collection sheets were distributed to the clinical supervisor for completion. Frequent phone calls were used to answer queries and ensure that data were correctly documented.

The dialysis patient questionnaire included social history, history of smoking, physical independency, detailed clinical history, presentation of ESKD and any history of hospitalisation at the time of initiation of dialysis, family history of CKD, history of previous blood transfusion (if yes, patients were asked about the frequency of transfusions). For patients treated with HD, other questions included: HD hours per week, history of receiving HD in another centre inside Libya or abroad, type and site of vascular access used for HD, history of previous vascular access-related complications and hospitalisations, mean pre-dialysis blood pressure over one week before the interview and erythropoietin treatment. Available recent investigation results were collected and recorded for all dialysis patients including: haematocrit, alanine aminotransferase and aspartate aminotransferase concentration, serum albumin and predialysis serum urea and creatinine concentrations.

The principal researcher was responsible for obtaining consent and undertaking interviews while the research team collected information by inspecting medical records as well as asking the treating staff about missing information.

3. 9. Follow up data

Follow-up included two types of data. First, follow-up and outcome data were collected for every patient included in from May to August 2009 study. Data was collected from August to December 2010. Variables were similar to those used during the cross-sectional study and similar data collection forms were used. Questions added included admission to hospital during the follow up year (and the reason for admission) and sero-conversion to HBV or HCV in previously sero-negative HD patients. The second set of data was brief demographic and clinical information of all new ESKD patients who joined dialysis facilities during the follow-up time (August to December 2010). The research team conducted data collection frequently during the year to ensure the inclusion of every new patient in the country. Subsequently, researchers conducted field visits to dialysis facilities from August to December 2010 to validate the information.

3. 10. Frequency of assessments and timing

Clinical supervisors of the maintenance dialysis facilities were interviewed once. Each personal interview took around 30 minutes while telephone interviews were generally shorter. Each patient receiving maintenance dialysis was interviewed twice while they were in the dialysis facility, first at recruitment and then again after 1 year. The first interview took approximately 30 minutes while the second was relatively shorter.

3. 11. Subjects and centre selection (inclusion criteria)

- All Libyan maintenance dialysis facilities (n=40) providing services during May to August 2009 were included in the initial study of dialysis provision.

- Regarding individuals, this study included all adult (16 years or older) patients receiving dialysis in Libya between May 2009 and December 2010.

3. 12. Statistical analysis

Information about the maintenance dialysis facilities on the questionnaire sheet was coded and entered into a spreadsheet for analysis using SPSS 16.0. (SPSS, Inc., Chicago, IL, USA). Descriptive analyses were employed as appropriate.

Information collected about maintenance dialysis- treated patients was revised and cross checked for patients who were known to receiving dialysis in another centre within the country. Data coded and entered into a spreadsheet for analysis using SSPS 16.0. (SPSS, Inc., Chicago, IL, USA). Data presented as mean, standard deviation if normally distributed or median (interquartile range) if not. A Chi-squared test was used to evaluate the significance of relations between categorical variables. Correlations were tested with a Pearson's test. A *t*-test was used to compare means between groups for data with normal distribution or Mann-Whitney test for non-parametric data. Multivariable binary logistic regression was used in certain analyses to identify independent determinants of dependent variables. A P-value of <0.05 was considered statistically significant.

3. 13. Data handling and record keeping

Information regarding study subjects is kept safe and confidential. Data were anonymised before entry into a computer database. Study subjects or individual dialysis facilities are not identifiable in any publications. The researcher maintains a study master file that contains all the essential documents relating to the study.

Chapter 4

Results

Provision and quality of dialysis services in Libya

4. Provision and quality of dialysis services in Libya

4.1. Introduction

The prevalence of ESKD is increasing worldwide. It is a chronic and irreversible condition associated with substantial morbidity, high mortality rates and large financial burden on health care systems (214-216). Dialysis remains the main technique for RRT due to a shortage of donated organs. Improving the quality of care for dialysis patients through standardisation is associated with favourable outcomes (217-219) and several professional organizations have developed evidence-based guidelines to optimize the quality of care (220).

Libya is a vast country with an area of 1,665,000 square kilometres (221). Its estimated total population was slightly over five and half million in 2009 (221). In spite of a low population density of three persons per square kilometre, the majority (85%) of the country's population are urban (222). Overall, it is classified as a medium- developed country in the United Nations Human Development Index (http://hdr.undp.org/en/statistics). Per capita purchasing power parity was estimated as $14,000 in 2010 which ranked the country as 83th compared to the world (https://www.cia.gov). However, about one-third of Libyans live at or below the national poverty line. Generally, development indicators are among the best in the African continent and above the mean for the Arab world (222). Dialysis services are offered free of charge to all referred patients regardless of their age. All dialysis facilities belong to the public sector and are funded by the Secretariat for Health and the Environment. Although dialysis has been provided in Libya for around 4 decades, no national dialysis practice guidelines are available to promote best practice. In fact, the provision of RRT in Libya has not been previously evaluated. Generally, there is lack of information about dialysis infrastructure and there is no renal registry to gather national data. This study was therefore undertaken to assess the provision and quality of current dialysis services in Libya to inform policy decision makers as well as caregivers and facilitate health care development in addition to the establishment of a Libyan renal registry.

4. 2. Methods

A cross-sectional study of all active Libyan dialysis centres was undertaken from May to August 2009. As there was no accurate list of names and contact information for dialysis centres in Libya, researchers contacted the national drug and medical supplies company to obtain a contact list. Disappointingly, even this list was deficient. Researchers subsequently contacted each general and specialized hospital in the country by phone and enquired about dialysis services within the hospital or in the region to complete the first comprehensive list of chronic dialysis units and contact details. Centres providing only acute dialysis were not included.

A structured questionnaire was designed to lead the interview. It included four main groups of questions: dialysis capacity, staffing, methods of assessment of dialysis patients and infection control measures. The questionnaire was tested in four dialysis centres and validated through discussion with the clinical directors of surveyed centres. Ethical approval for the study was obtained from the Libyan National Committee for Bioethics and Bio-safety.

Medical directors of dialysis units were contacted initially by phone, informed about the study and asked to participate by answering the questions either by phone or by face to face interview. All directors (n=40) agreed to participate in the study and 28 agreed to a face to face interview. Each personal interview took around 30 minutes while phone interview was generally shorter. Each principal contact was interviewed once. Further telephone calls were made to almost all centres to collect missing data, mostly recent statistics regarding patients and staff. In all dialysis centres visited, the head of the facility invited researchers to view the facility.

Information on the questionnaire sheet was coded and entered into a spreadsheet for analysis using SPSS 16.0. Descriptive analyses were employed as appropriate.

4. 3. Results

4. 3. 1. Dialysis capacity

The first HD service in Libya was opened in Aljemhoria Hospital in Benghazi city in 1973. The number of patients and centres has increased over time (figure 4. 1). PD was introduced to Libya as a trial in the late 1990's but utilisation has remained minimal.

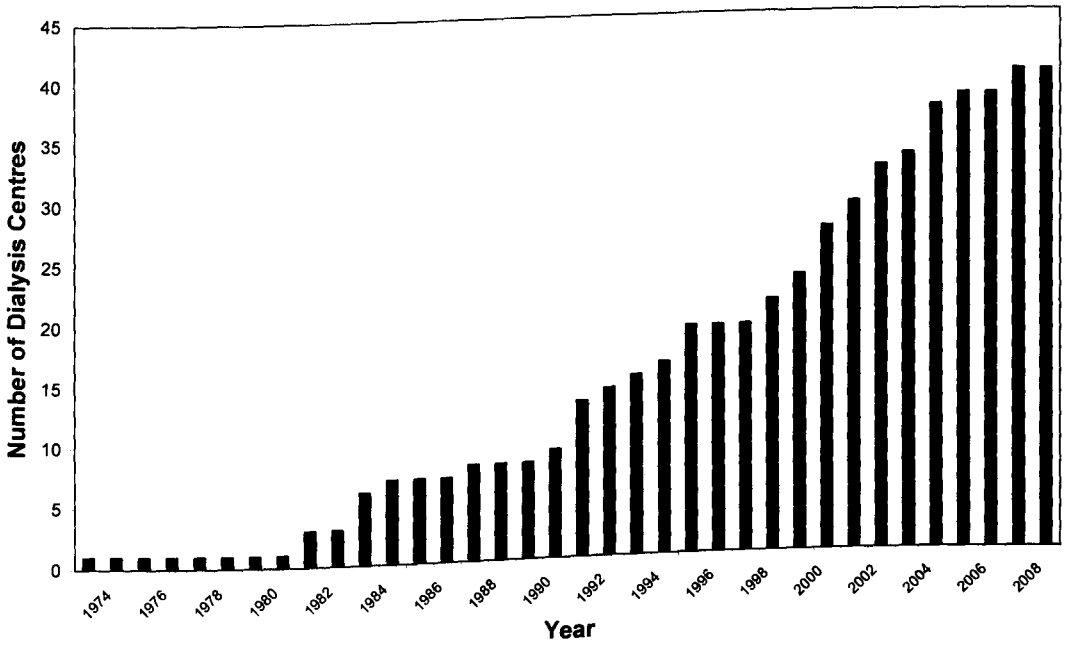

Figure 4. 1: Increase in dialysis centres over time in Libya.

Table 4. 1 describes dialysis service capacity. A total of 2417 adult patients (approximately 60 patients/ centre) were receiving maintenance dialysis therapy in 40 centres. The estimated population of Libya during 2009 was 5,488,444 (of which 29.4% were <15 years) giving an estimated adult population of 3,874,841. The prevalence of ESKD treated with dialysis in adult population of Libya was therefore approximately 624 pmp in the year 2009.

Most dialysis patients (98%) were Libyans and the majority were over 15 years of age (98.8%). Median age of prevalent patients was 49 years (inter-quartile range 36-61 years). Median dialysis vintage was 3 years (inter-quartile range 1-6 years). Thirty-two (80%) dialysis units were located in the northern part of the country (mainly the coast, western and eastern mountainous regions) where 88.5% of inhabitants live. Thirty-five dialysis units (88%) were placed within a local hospital campus whereas 13% were free standing centres. Most centres (83%) accepted a mix of paediatric and adult patients (age range 8-90 years). However, 15% of dialysis centres treated only adult patients and one facility treated children only (age range 3-17 years). Amongst dialysis centres, just three offered PD in the form of continuous ambulatory PD (CAPD) and all were located in the north. No automated PD and no home HD are currently offered.

Dialysis shifts were 4 per day in one centre only, 3 per day in 7 (17%), 2 per day in 21 (52%) and one per day in 11 (27%). HD shifts generally started at around 7:00 am. Facilities that run evening shifts usually end by 10:00 pm. One centre scheduled treatments at night from 10:00 pm to 2:00 am to accommodate a rise in number of patients requiring dialysis. Most large centres accepted new patients immediately and scheduled or referred them to another centre after stabilizing their condition. Dialysis facilities had different designs and room sizes. Table 4. 1 shows that the total number of HD rooms was 192 (range 1-21 rooms per facility). They hosted 713 functioning HD stations (range 1-90 per facility), with a ratio of one machine to 2.8 patients. The total number of non-utilised HD machines was 130. Of these 109 needed repairs whereas the remainder were kept as a reserve. The majority of patients were offered HD 3 times a week. However, 6 facilities could not provide regular slots for new patients and they were therefore initially dialysed infrequently when slots were available. Most centres modify the frequency of treatment according to patients' medical condition and attendance.

All centres provided free supplies of adjunctive treatments for dialysis patients including those administered at the dialysis centres like erythropoietin and those which are administered at home such as iron, folic acid, vitamin D and calcium. However, all units experienced intermittent shortages of most types of medications. A service for creation of permanent vascular access was available locally in just 6 centres (15%). In the majority of centres patients were referred to vascular surgeons elsewhere.

Table 4. 1: Description of dialysis services in different regions of Libya.

		Regions			
		North West N=21 (%)	**North East N=11 (%)**	**South N=8 (%)**	**Total N=40 (%)**
Total number of adult patients		1558	653	206	2417
Prevalence 2009 (adults pmp)		628	623	597	624
Dialysis centres located in hospital campus		18 (86)	10 (91)	7 (88)	35 (88)
Dialysis provided for both adults and children		17 (81)	9 (82)	8 (100)	34(85)
Centres provide both haemodialysis and peritoneal dialysis		2 (10)	1 (9)	0 (0)	3 (8)
Median number of working days/week		6	6	6	6
[Range]		[3-7]	[5-6]	[3-6]	[3-7]
Working shifts/ day	One	3	5	3	11 (27)
	Two	11	5	5	21 (52)
	Three	6	1	0	7 (17)
	Four	1	0	0	1 (2)
Number of dialysis rooms		106	60	26	192
Number of all haemodialysis stations		490	253	100	843
Number of working haemodialysis stations		429	212	72	713
Median number of working haemodialysis station/centre		20	16	7	15
[Range]		[1-90]	[4-61]	[4-23]	[1-90]
Haemodialysis stations to patients		1:3.2	1: 3.1	1:2.9	1:3.4
Local vascular access surgery		3 (14)	3 (27)	0 (0)	6 (15)
Availability of educational materials		6 (29)	3 (27)	0 (0)	9 (23)

4. 3. 2. Staffing of dialysis facilities

Table 4. 2 shows that a nephrologist or a physician was available on call for all dialysis sessions in 95% of centres. Approximately half of dialysis centres offered scheduled specialist consultations in outpatient clinics. Two remote centres in the South were delivering services without any doctors due to lack of staff. The total number of national and non-national doctors was 114 (doctor to patient ratio 1:22). Among these, there were 53 junior physicians and 61 qualified nephrologists/internists (nephrologist/internist to patient ratio 1:40). The overall number of trained dialysis nurses was 639 with a ratio of one nurse to 3.7 patients. Social workers and dieticians were available in 15 and 20% of dialysis facilities, respectively.

Table 4. 2: Staffing of dialysis centres in different regions of Libya

	Regions			
	North West N=21 (%)	**North East N=11 (%)**	**South N=8 (%)**	**Total N=40 (%)**
Centres with physician available on call at all dialysis sessions	21 (100)	11 (100)	6 (75)	38 (95)
Outpatient nephrology consultation	10 (48)	8 (73)	3 (38)	21 (53)
Total number of junior doctors in region	39	9	5	53
Median	1	0	0.5	1
[Range]	[0-10]	[0-3]	[0-2]	[0-10]
Total number of nephrologists/ internists in region	32	25	4	61
Median	1	2	0	1
[Range]	[0-4]	[0-6]	[0-2]	[0-6]
Nephrologists/Internists to patient ratio	1: 49	1: 26	1: 52	1: 40
Total number of trained dialysis nurses	379	169	93	641
Median	15	11	11	11.5
[Range]	[2-90]	[4-72]	[6-26]	[2-90]
Nurse to patient ratio	1:4	1:4	1:2	1: 3.7
Presence of social workers	5 (24)	1 (9)	0 (0)	6 (15)
Presence of dieticians	4 (19)	3 (27)	1 (13)	8 (20)

4. 3. 3. Assessment of maintenance dialysis patients

Findings related to methods employed to monitor patients are described in table 4. 3. KDOQI guidelines were applied in only 4 dialysis centres. Pre, intra and post dialysis blood pressure were recorded routinely in all dialysis facilities as well as pre and post dialysis weight measurement. HD adequacy was monitored by Kt/v measurement in some patients in 10% of centres, whereas urea reduction ratio was used in 25% of centres. The remaining 28 centres including all centres in the south used a single monthly pre-dialysis urea measurement to monitor adequacy. Haemoglobin and haematocrit were monitored monthly in all centres. Only 40% of centres had an established policy for anaemia monitoring by measuring serum ferritin and total iron binding capacity (TIBC). Another 15% assessed anaemia by measuring serum iron and TIBC. Mineral metabolism was evaluated by measurement of serum calcium and phosphorus in 85% of centres and by serum calcium only in 5%. No assessment of blood minerals was performed in 10%. Monitoring serum albumin as an indicator of nutritional status was done monthly in 58% of centres. Finally, parathyroid hormone levels were assessed in 13% of centres. However, all centres experienced intermittent deficiency in laboratory supplies resulting in failure to perform required blood tests.

Table 4. 3: Monitoring of dialysis patients in different regions of Libya.

	Regions			
	North west	**North east**	**South**	**Total**
	N=21 (%)	**N=11 (%)**	**N=8 (%)**	**N=40 (%)**
Application of dialysis practice guidelines	3 (14)	1 (9)	0 (0)	4 (10)
Pre, intra& post dialysis measurement of blood pressure	21 (100)	11 (100)	8 (100)	40 (100)
Pre& post dialysis measurement of weight	21 (100)	11 (100)	8 (100)	40 (100)
Monitor HD adequacy by Kt/v	3 (14)	1 (9.1)	0 (0)	4 (10)
Monitor HD adequacy by urea reduction ratio	5 (24)	2 (18)	0 (0)	7 (18)
Monitor anaemia by testing HB, HCT, serum ferritin and total iron binding capacity	10 (48)	5 (45)	1 (13)	16 (40)
Monitor serum calcium and phosphorus	18 (86)	10 (91)	6 (75)	34 (85)
Monitor of serum albumin	13 (62)	7 (64)	3 (38)	23 (58)
Monitoring of Parathyroid hormone	3 (14)	1 (9)	1 (13)	5 (13)

4. 3. 4. Infection control measures

Facilities for isolation of patients with chronic viral infections were not available in all centres. All centres routinely screened patients for HBV, HCV and HIV infection every 3-6 months and upon transfer from another dialysis facility. Table 4. 4. shows that separate rooms were allocated for patients who were seropositive for chronic viral infection in 93% of the units while a dedicated machine/s in a common room were reserved for infectious patients in the remaining 7%. Vaccination against HBV was available for staff in all centres and for patients in 65%. Hand wash facilities were available in each HD room in 22 centres (55%). No dialyzer reuse was permitted in any centre despite a relative shortage of high flux dialyzers. Machine disinfection was performed routinely after each dialysis session in all dialysis facilities. Samples of water for biological quality testing had been collected during the preceding year in one quarter of centres. However, no analysis reports were found in any centre. Chemical quality of HD water was not tested in any centre. Sharps separation was routinely practiced by 90% of dialysis centres. Facilities for treatment of hospital waste were available in only 9 centres.

Table 4. 4: Description of infection control measures in dialysis centres in different regions of Libya.

		Regions			
		North west N=21 (%)	**North east N=11 (%)**	**South N=8 (%)**	**Total N=40 (%)**
Isolation of chronic viral infection sero-reactive patients in special rooms		18 (86)	11 (100)	8 (100)	37 (93)
HBV vaccine for patients		10 (48)	9 (82)	7(88)	26 (65)
Hands wash facility in each haemodialysis room		12 (57)	6 (55)	4 (50)	22 (55)
Water quality tests performed during the preceding year	Biological	6 (29)	3 (27)	1 (13)	10 (25)
	Chemical	0	0	0	0
Separation of sharps		20 (95)	10 (91)	6 (75)	36 (90)
Waste disposal	Domestic	14 (67)	10 (91)	7 (88)	31 (78)
	Incineration	7 (33)	1 (9)	1 (13)	9 (23)

4. 4. Discussion

This study attempted to gather baseline information about the structure and quality of dialysis services in Libya in order to promote improvement and facilitate the development of a renal registry as well as to initiate further studies in the country. A renal registry represents a valuable resource for auditing services and provides regular performance feedback to dialysis centres as well as health care authorities (179, 223).

This study shows for the first time, that Libya has a relatively high prevalence rate of ESKD patients treated with dialysis (table 4. 5). It is higher than rates reported in countries like Philippines, Romania, Thailand and the UK (224, 225). This rate is double the average rate estimated for the Mediterranean region of 312-352 pmp (24, 25). Furthermore, it is approximately one third higher than the rate reported in Saudi Arabia (19). The provision of dialysis has increased in Libya in the decades since it was introduced. The need for this service is expected to grow further: first, because of increasing prevalence of classical risk factors for ESKD in the community (190, 226), second, because of weak PHC and absence of screening programmes which slow the progress of CKD to ESKD (222) and third, due to limited renal transplantation services as Libya is exclusively dependent on the live related donors (205). Kidney transplantation was introduced into the country as a collaborative project between Poland and Libya in 1988. Polish surgeons transplanted 63 kidneys from live related donors during 8 years. Eventually, transplantation activities totally collapsed, largely due to United Nation's sanctions against Libya and subsequent shortage of the immunosuppressive therapy and medical equipments. Lately, in 2004, renal transplantation activates was initiated in a sole centre in Tripoli with a capacity of approximately 45 live- related renal transplants per year. This restricted access to renal transplantation increases dialysis dependency because most patients fail to provide a suitable enthusiastic relative. A deceased organ donation program has been initiated in the country, but is still hampered by lack of proper knowledge, religious misconception and other psychological factors (207).

Table 4. 5: Prevalence rates of dialysis per million population in different countries/regions.

Country/ region	Prevalence rates of dialysis per million population	Year
Taiwan	2288	2007 (224)
United States	1159	2008 (224)
Libya	624	2009
Saudi Arabia	475	2009 (19)
UK	411	2008 (225)
Thailand	363	2007 (224)
Romania	345	2007 (224)
Mediterranean region	312- 352	2006- 2008 (24, 25)
Bangladesh	99	2007 (224)
Philippines	74	2007 (224)

Although CAPD is a popular method for treating ESKD in many countries (227) there were only 3 centres offering CAPD which served 35 patients. The total number of active PD patients in the Middle East was recently estimated to be approximately 8170, representing around 10.2% of overall dialysis population in the region (25). Most were in Turkey, Iran and Saudi Arabia who have well established programmes (25).

There were wide discrepancies in the working capacity between different centres in different regions of Libya. Some facilities were overloaded with patients while others were running just a few sessions per week. Most facilities did not operate at full working capacity with each machine serving only 3- 4 patients per week. In contrast, most dialysis units in France (228) and England (229) operate at near maximal HD capacity. This observation raises the importance of integrated health care planning and the lack of a national standard for the number of dialysis stations per population. The data presented will inform decisions about improving dialysis infrastructure and future expansion.

Despite the provision of modern HD machines, weak technical support especially in remote centres resulted in an accumulation of non-functioning HD machines (15.4% of total number of machines) and waste of health care resources. The deficiency was more pronounced in the

southern dialysis centres where 28% of machines were non- functioning. There is therefore an urgent need to improve technical support to dialysis centres.

Permanent vascular access in the form of an AVF or AVG is the safest and most cost effective way to perform HD (59). Our data show that surgical services for creation of a fistula were limited to a few centres where vascular surgery staff and equipment were available. Many patients have to travel long distances and wait variable periods of time before getting their vascular access surgery. Centres in the southern region were most affected. Expansion of services for vascular access provision is therefore an important priority.

All dialysis staff in Libya are recruited, paid and supervised by the Secretariat for Health and the Environment. Our results show an overall staffing ratio of one nephrologist/ internist to 40 patients. This ratio is greater than that reported in the United States and France (1:48) (180, 228) and far greater than New Zealand (1:102) (230). The distribution of senior qualified nephrologists in Libya varies widely between regions. However, this number does not reflect the actual care delivered to dialysis patients because they are usually engaged in multiple tasks including nephrology outpatient clinics, dialysis follow up, inpatient care and medical teaching. Despite the enormous growth of the healthcare sector in Libya, specialised physicians are still deficient in certain fields including renal medicine. This deficiency might be attributed to defective planning of graduate educational courses on one hand and migration of qualified staff (brain drain) on the other (193). The 53 junior dialysis physicians identified in this study were new medical graduates who lack necessary knowledge and experience. These new physicians work in dialysis centres as a part of their general medicine training programme for a maximum period of 6 months. More research is required to determine the actual nephrologist-patient contact time and dialysis patient satisfaction in order inform decisions regarding optimal staffing levels. Regarding nursing staff, our data show adequate nurse to patient ratios. As in most countries, nurses deliver most of dialysis patient care (231). Many health care institutes in Libya provide training programmes for dialysis nurses. Conversely, our results show a marked deficiency of social workers and dieticians despite their important role in dialysis patient care (232, 233).

In Libya, there are no national dialysis practice guidelines and few clinical practitioners were familiar with KDOQI guidelines. This lack of national guidelines has resulted in variable approaches to patient management and monitoring. The majority of centres rely on clinical monitoring and monthly pre-dialysis urea readings which probably do not reflect urea clearance since low values may be a sign of poor nutrition. Similar problems have been observed in Saudi Arabia prompting calls for guidelines to optimize dialysis delivery in that country (234). Online measurement of urea removal by Kt/v is available on most HD machines used in Libya. There is therefore the potential to substantially improve the quality of monitoring through national guidelines. In addition to lack of uniform standards, monitoring of patients was adversely affected by intermittent shortage of some laboratory reagents. Similarly, the supply of medication and high flux dialyzers was subjected to repeated interruption in almost all facilities.

Dialysis centres in Libya generally apply a strict infection control policy including; screening patients for blood borne infections, liberal use of non-sterile gloves, machine disinfection, no dialyzer reuse, maintenance of hygiene and vaccination of staff against HBV. However, nearly half of facilities lacked hand washing facilities in dialysis rooms. This was either because of faulty design or as a result of converting rooms built for other purposes into HD rooms to accommodate increasing numbers of patients. Hand disinfectant was available in most HD rooms and was routinely used by staff. Studies are needed to determine prevalence rates of blood borne infections in dialysis patients as well as the rate of sero-conversion of negative patients to provide better data regarding the effectiveness of infection control measures. Separation of sharps was not practiced by 10% of Libyan dialysis centres. However, even after separation of sharps, the large amount of potentially infective waste generated from dialysis practice was mostly treated as domestic waste by dumping or open air burning. The technology needed for management of hospital waste is limited and should be improved.

Libya faces strong constraints in terms of access to fresh water due to perpetual drought (235). Many dialysis centres were obligated to dig their own wells to maintain water supply. However, testing water quality was not regularly practiced despite reports about ground water pollution (236). All Libyan dialysis centres have water treatment plants but samples of dialysis water were collected from only a quarter of dialysis facilities. Even in these facilities no

laboratory reports were returned for feedback. Again, there were no dialysis water reference standards to guide practitioners.

4. 5. Conclusion

Dialysis (mainly HD) services are appropriately distributed to serve almost all populated regions and are funded by Libyan government. In spite of large geographic area, the provision of dialysis appears adequate but there is a wide discrepancy in methods applied to manage and monitor patients. Several areas for improvement have been identified including a need for more efficient use of existing facilities, promotion of more uniform dialysis practices by guidelines, improved technical support, establishment of a Renal Registry, recruitment of more nephrologists, enhancing infection control measures, improving reliability of distribution networks for dialysis and laboratory supplies as well as drugs, monitoring quality of HD water and the development of more cost-effective alternatives such as PD and transplantation.

Chapter 5

Results

Epidemiology and aetiology of dialysis-treated end-stage kidney disease in Libya

5. Epidemiology and aetiology of dialysis-treated end-stage kidney disease in Libya

5.1. Introduction

ESKD is highly prevalent globally. It has become a major public health problem and is associated with considerable co-morbidity and mortality. Maintenance dialysis therapy is the commonest mode of RRT and demand for this service is increasing progressively worldwide.

Libya is a sparsely populated medium-developed country but it has a high prevalence of risk factors for CKD such as diabetes, hypertension and obesity (188, 226, 237, 238). Societal, economic and environmental transformation have contributed to people tending to adopt a sedentary life (239). Attention paid by the PHC systems to combat the rising epidemic of chronic diseases has been inadequate (240). In contrast, Libya was among the first countries in the region to establish free access to maintenance dialysis therapy for patients with ESKD (241). Health care administrative bodies have continued to expand dialysis services in terms of geographic coverage and capacity to cope with increasing demand (241). Kidney transplantation in Libya is limited by the lack of cadaveric donors and limited availability of suitable living-related donors (203, 204). Thus the majority of patients with ESKD remain dialysis dependent. Nevertheless, data regarding the epidemiology of ESKD and dialysis treatment in Libya are scarce and knowledge about the spectrum of renal diseases is very limited. The purpose of this study was to develop the first comprehensive description of the epidemiology of dialysis-treated ESKD in Libya. The study was performed prior to the recent conflict but as Libya prepares to redevelop its healthcare system these data will be vital to guide strategies for the prevention of CKD and planning for the provision of RRT.

5. 2. Methods

The study was performed by a Libyan researcher with support and guidance provided by a Nephrology Department in the UK. First, a cross-sectional study was performed from May to August 2009. This included all adult maintenance dialysis facilities in Libya (n = 39), One

paediatric dialysis facility was excluded. All dialysis facilities belong to the public sector. Medical supervisors of maintenance dialysis facilities throughout the country were contacted by visit or phone call to be informed about the study. All agreed to participate and to cooperate with the research team.

A data collection sheet was prepared and used to gather information about all currently registered dialysis patients in the country. Forms included data regarding date of birth, sex, ethnicity, nationality, type of dialysis, date of dialysis initiation and primary kidney disease. Date of birth was recorded if known. Otherwise, the year of birth was used. The same applied for the date of first dialysis. Primary kidney disease was recorded according to the opinion of the treating physician or medical reports when available.

For the majority of dialysis units (n = 28), the research team collected all information by interviewing patients and inspecting medical records to assure quality and validity of the data. For remote facilities, data collection sheets were distributed to the clinical supervisor for completion. Frequent phone calls were used to answer queries and ensure that data were correctly documented. A pilot study was undertaken in 5 dialysis units that included 100 patients (20 from each unit). Difficulties in collecting data were explored and solutions developed. Data were cross checked for patients who were known to receiving dialysis in another centre within the country. Patients who were absent at the time of the study for a period of less than one month for travel in or outside the country were included among the prevalent population. Analyses performed included all adult patients prevalent on dialysis on 30 August 2009.

Population estimates were obtained from the Libyan national statistics department. The age and gender breakdown of the population in each region was obtained from mid-2009 population estimates based on 2006 census data. The number of dialysis patients was calculated for the country as a whole. In order to investigate geographic variation in the epidemiology of ESKD, data were also grouped into 3 main geographic regions.

The second stage of the study was a prospective collection of information about all new patients who started dialysis from September 2009 to August 2010. Variables collected were identical to that used during the cross-sectional study and the same data forms were used. The

research team conducted data collection frequently during the year to ensure the inclusion of every new patient in the country. Subsequently, researchers conducted field visits to dialysis facilities from August to December 2010 to validate the information.

Data are presented as mean± standard deviation if normally distributed or median (interquartile range) if not. A Chi-squared test was used to compare frequencies between groups. A p-value of <0.05 was considered statistically significant. Analysis was performed by using SPSS version 16.0.

Permission to conduct the study was granted by the Ministry of Health. Ethical approval for the research was obtained from the Libyan National Committee for Bioethics and Bio-safety. Patients each gave written informed consent.

5. 3. Results

5. 3. 1. Prevalence of ESKD in Libya

As shown in Table 5. 1, the total number of adult ESKD patients undergoing maintenance dialysis therapy in Libya was 2417 in August 2009. The estimated adult population of Libya during 2009 was 3,873,000, giving a prevalence of dialysis-treated ESKD of approximately 624 pmp. The prevalence rate varied slightly by region with the highest rate of 628 pmp in North West region, the most populated area of the country. Most prevalent patients were under 65 years of age (85%). Female patients tended to be older than males, except in the south. Duration of dialysis was a median of 3 years and tended to be higher in females (Table 5. 2). The majority of dialysis patients were Libyan nationals (97.8% of prevalent and 96.6% of incident patients).

Table 5. 1: Prevalent and incident dialysis patient numbers and rates for Libya and its regions

	Regions			Whole country
	North West	North East	South	
Number of prevalent patients 2009	1558	653	206	2417
Prevalence rate 2009 (pmp)	628	623	597	624
Number of incident patients 2010	593	287	213	1093
Incidence rate 2010 (pmp)	239	274	617	282

Table 5. 2: Age, age at onset and dialysis vintage for prevalent and incident dialysis patients in Libya and its regions. Data are median and interquartile range

		Region				Total
		North West (n = 1558)	North East (n = 653)	South (n = 206)		
Age of prevalent patients in years (n = 2417)	Male	49	46	49	48	49
		36-61	35-59	36-61.3	36-61	36-61
	Female	49	50.5	42.5	49	
		34-60	37-61	32.3-59	35-61	
Age at onset of dialysis (n = 2417)	Male	45	42	47	44	45
		31-58	28-55	31-59.9	30-58	30-58
	Female	45	46	38	45	
		30-57	31-57	27-57.8	30-57	
Dialysis vintage in years (n = 2417)	Male	3	3	2	2.5	3
		1-6	1-7	0.1-4	1-6	1-6
	Female	3	3	2	3	
		1-5	1-6	2-2	1-6	
Age of incident patients in years (n = 1093)	Male	50	47	46	48	49
		37-63	34-61	30-57	35-61	35-62
	Female	52	53	43	50	
		35-66	41-64	36-54	36-64	

Figure 5. 1, shows that the prevalence of dialysis-treated ESKD was higher among males versus females at all ages. Overall, males represented 58% of prevalent dialysis population. The prevalence of ESKD varied considerably with age. Prevalence rates were low in young adults but showed a steady increase with age. Prevalence rates peaked in the 55–64 year age group at 2475 pmp for males and 2197 pmp for females. After age 74 years there was a sharp decline in prevalence and very few patients were over 85 years. Most prevalent patients on dialysis were white ethnicity (87%). However, ethnic distribution varied between regions with the highest black to white ratio of 1.9 to 1 in the South.

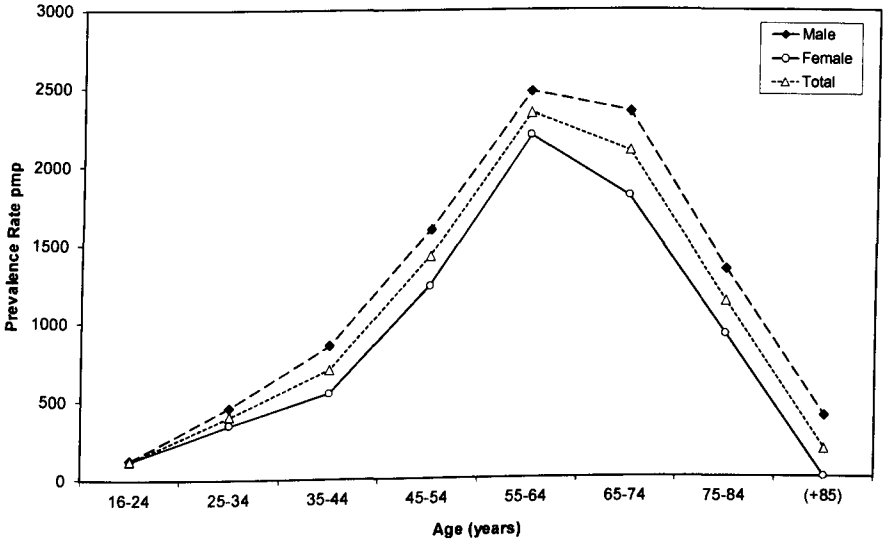

Figure 5. 1: Prevalence rate pmp of dialysis-treated ESKD in Libya for males and females by age group (males and females are a proportion of the gender specific in a million population)

5. 3. 2. Incidence of ESKD in Libya

A total of 1093 new patients started dialysis during the 1-year observation period, giving an incidence rate of 282 pmp. Incidence rates varied between regions with a substantially higher rate observed in the South (Table 5. 1). In most age groups the incidence rate was higher in males than females (figure 5. 2). The incidence rate increased with age until it peaked in those aged 65–74 years and decreased sharply beyond age 75 years. Incident female patients were slightly older than male patients. Most incident patients on dialysis were white (80.9%).

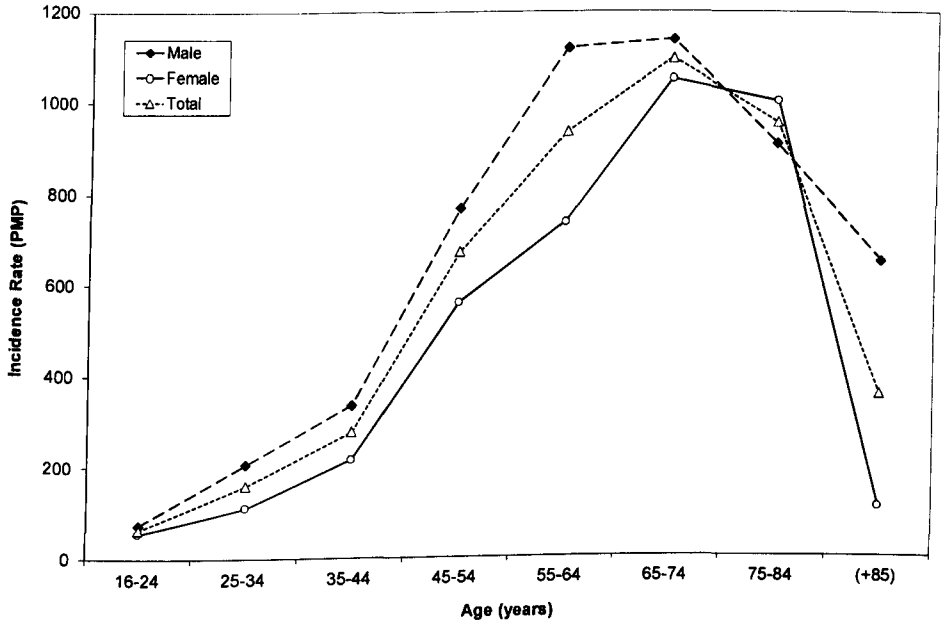

Figure 5. 2: Incidence rate pmp of dialysis-treated ESKD in Libya for males and females by age group (males and females are a proportion of the gender specific in a million population)

5. 3. 3. Aetiology of ESKD in Libya

Information about primary kidney disease was complete for all prevalent dialysis patients but was missing in 75 (6.9%) of incident dialysis patients. Data are shown in tables 5. 3 and 5. 4. The most common cause of ESKD among prevalent and incident patients was diabetes. The frequency of different categories of pathology was similar for prevalent and incident patients. Diabetes and hypertensive nephropathy were more common as causes of ESKD in patients aged 50 years or older whereas glomerulonephritis and hereditary diseases were more common in those aged under 50 years. Autoimmune diseases accounted for only a small proportion of all ESKD and were more common among females.

Table 5. 3: Aetiology of primary kidney disease of prevalent dialysis patients according to gender and age

Primary kidney disease	Gender		Age		All patients
	Male (n = 1402)	Female (n = 1015)	<50 years (n = 1268)	≥50 years (n = 1149)	(n = 2417)
Diabetic Nephropathy	396 (28.2)*	245 (24.1)	169 (13.3)*	472 (41.1)	641 (26.5)
Hypertensive Nephropathy	180 (12.8) *	173 (17)	129 (10.2)*	224 (19.5)	353 (14.6)
Glomerulonephritis	318 (22.7) *	194 (19.1)	413 (32.6)*	99 (8.6)	512 (21.2)
Interstitial Nephritis	14 (1)	15 (1.5)	17 (1.3)	12 (1)	29 (1.2)
Obstructive Nephritis	78 (5.6)	42 (4.1)	59 (4.7)	61 (5.3)	120 (5)
Chronic pyelonephritis	19 (1.4) *	29 (2.9)	33 (2.6) *	15 (1.3)	48 (2)
Polycystic kidney disease	82 (5.8)	70 (6.9)	68 (5.4)	84 (7.3)	152 (6.3)
Congenital and hereditary diseases	168 (12) *	130 (12.8)	220 (17.3)*	78 (6.8)	298 (12.3)
Autoimmune diseases	4 (0.3) *	13 (1.3)	16 (1.3) *	1 (0.1)	17 (0.7)
Other	39 (2.8)	32 (3.2)	48 (3.8) *	23 (2)	71 (2.9)
Unknown	104 (7.4)	72 (7.1)	96 (7.6)	80 (7)	176 (7.3)

Data are number (percent)
*P < 0.05 versus comparison group

Table 5. 4: Aetiology of primary kidney disease of incident dialysis patients according to gender and age

Primary Kidney Disease	Gender		Age		All patients
	Male (n = 621)	Female (n = 397)	<50 years (n = 521)	≥50 years (n = 497)	(n = 1018)
Diabetic Nephropathy	173 (27.9)	116 (29.2)	90 (17.3)*	199 (40)	289 (28.4)
Hypertensive Nephropathy	101 (16.3)	60 (15.1)	29 (5.6)*	132 (26.6)	161 (15.8)
Glomerulonephritis	133 (21.4)	71 (17.9)	173(33.2)*	31 (6.2)	204 (20)
Interstitial Nephritis	7 (1.1)*	17 (4.3)	14 (2.7)	10 (2)	24 (2.4)
Obstructive Nephritis	53 (8.5)*	6 (1.5)	17 (3.3)*	42 (8.5)	59 (5.8)
Chronic pyelonephritis	9 (1.4)	4 (1)	0 (0)*	13 (2.6)	13 (1.3)
Polycystic kidney disease	13 (2.1)*	41 (10.3)	31 (6)	23 (4.6)	54 (5.3)
Congenital and hereditary diseases	42 (6.8)	40 (10.1)	73 (14)*	9 (1.8)	82 (8.1)
Autoimmune diseases	4 (0.6)*	10 (2.5)	11 (2.1)*	3 (0.6)	14 (1.4)
Other	10 (1.6)	4 (1)	10 (1.9)	4 (0.8)	14 (1.4)
Unknown	76 (12.2)*	28 (7.1)	73 (14)*	31 (6.2)	104 (10.2)

Data are number (percent)
*P < 0.05 versus comparison group

5. 4. Discussion

This study represents the first comprehensive description of the epidemiology of dialysis-treated ESKD in Libya. Our study shows a prevalence rate for ESKD markedly higher than rates estimated for the Mediterranean region of 312 to 352 pmp (24, 25) despite similar demographic and socioeconomic characteristics between Libya and neighbouring countries. Libya's prevalence rate is also higher than rates reported from individual countries in the region like Saudi Arabia (475 pmp) (19), El-Minia city in Egypt (208 pmp) (26), Kuwait (240 pmp) (24) and Oman (220 pmp) (24). Reasons for the high prevalence rate in Libya might include a high prevalence of CKD in the population and limited access to renal transplantation (204, 242). The high incidence rate of ESKD observed in this study (282 pmp) supports the notion that CKD is an important health problem in Libya that requires urgent attention. The rate is

more than double that observed in European countries such as Austria (131 pmp) (243) and Denmark (129 pmp) (243) despite the fact that the Libyan population is younger than that of most European countries. Moreover, the incidence rate observed in Libya is even higher than rates reported in other places with young populations such as Qatar (202 pmp) (16), Tunisia (159 pmp) (17), Bhopal city in India (151 pmp) (18), Malaysia (138 pmp) (244), Saudi Arabia (122 pmp) (19), Jordan (111 pmp) (20) and Aleppo city in Syria (60 pmp) (21). Whereas the prevalence rate did not vary by much in the different geographic regions of Libya the observed incidence rate was substantially higher in the South. Regional variation in incidence of ESKD has been reported by other authors (185, 245). The reasons for this variation in Libya require further investigation and have important implications for future healthcare provision. The South of Libya is a remote, sparsely populated and deprived area. It is also hot and dry and is inhabited by a mixture of different minorities such as black Arabs, Tuareg and Tebou tribes. Thus geographic, racial and socioeconomic factors may all be relevant. It is also notable that the proportion of new patients who commenced dialysis therapy in one year represents 45% of the number of prevalent dialysis patients in Libya. Moreover in the South the incidence rate was triple the prevalence rate. Possible explanations for these observations include a high mortality rate on dialysis or rapidly increasing incidence of ESKD. Both possibilities require urgent investigation and have serious implications for future demand for dialysis in Libya.

The median age of prevalent patients revealed by this study was substantially lower than that observed in other countries including the UK (65.9 years for HD and 61.2 years for PD) (246), United States (59.1 years) (224), Iceland (64.4 years), Austria (60.1 years), Denmark (58.8 years) and Greece (58.1 years) (243). The majority of patients with ESKD in Libya are of economically active age and ESKD therefore has a significant impact on families and society. The observed median age for incident patients in Libya (49 years) was considerably lower than the UK (64.8 years) (12). Consistent with studies from most other countries, males outnumbered females in the prevalent and incident populations (224, 247, 248). Nevertheless, the median age of incident females in the South was a decade younger than females in other regions of the country. This wide range of age presentation in the South might reflect gender inequity, health care deficiency and environmental factors.

Like many other countries diabetic nephropathy was the leading cause of ESKD in both prevalent and incident dialysis populations and was significantly more common among older patients. Generally, the prevalence of diabetes in Middle East region is high according to the International Diabetes Federation (249, 250). Reasons include increasing urbanisation, aging of the population, increasing obesity and falling levels of physical activity (251, 252). Efforts to reduce the burden of ESKD in Libya should therefore focus on measures to reduce incidence of type 2 diabetes mellitus (55, 253) through public awareness, screening and promotion of a healthy lifestyle as well as prevention of microvascular complications in those with diabetes (254). Glomerulonephritis was the second most frequent cause of ESKD in Libya in prevalent and incident cases and was significantly more common among young and male patients. The observed proportion is midway between very high levels reported from countries like China and Kuwait of approximately 35% (43, 44), Costa Rica (30%) (45) and Yemen (25%) (46) and lower prevalence observed in countries like Qatar (13%) (16), Sri Lanka (12%) (47) and Pakistan (10%) (48). Reasons for the high prevalence of glomerulonephritis require further investigation, which is hampered by the shortage of facilities able to perform renal biopsies and histology. A substantial proportion of ESKD was attributed to hypertension but it is unclear what proportion of this represented hypertension secondary to primary renal disease. Congenital and hereditary kidney disease accounted for a significant minority of ESKD in both prevalent and incident patients. This is likely due to the high rate of marriages between relatives, especially first cousins, in Arab communities (52, 255, 256) including Libya. A shortage genetic diagnostics and counselling is a major contributor to this problem. In summary, despite Libya's unique social and demographic features the observed causes of ESKD are similar to that described in most other countries, though the contribution of glomerulonephritis and hereditary kidney disease is greater than in many developed countries. It is therefore likely that interventions that have proved successful in reducing the incidence of ESKD in other countries such as early detection of CKD, treatment of hypertension with angiotensin-converting enzyme inhibitors and prevention or treatment of diabetes are likely to be effective in Libya too.

Strengths of this study are the inclusion of all current dialysis units in the country to ensure collection of the most complete data possible and prospective capture of data regarding new patients commencing dialysis. Limitations include reliance on limited and partially incomplete medical records and lack of histology to confirm the cause of ESKD in the majority of cases. We have described the epidemiology of ESKD among patients receiving dialysis but there are no data regarding patients with ESKD who died without the benefit of dialysis. It is therefore likely that the true incidence of ESKD is higher than what we have observed. Further research is required to investigate how many patients with ESKD are not offered dialysis and the reasons for this.

5. 5. Conclusions

In conclusion we report for the first time high prevalence and incidence rates of dialysis-treated ESKD in Libya. The relatively young age of those affected emphasizes the need for urgent measures to reduce the incidence of CKD and its progression. Emphasis should be placed in the first instance on the prevention and treatment of diabetes and hypertension. Further research is required to investigate the high incidence of glomerulonephritis. As Libya rebuilds its healthcare system following the recent conflict it is hoped that the prevention of ESKD will constitute an important priority and that the data presented will inform the strategies required.

Chapter 6

Results

Hepatitis B and C infection in haemodialysis patients in Libya: Prevalence, Incidence and Risk Factors

6. Hepatitis B and C infection in haemodialysis patients in Libya: Prevalence, Incidence and Risk Factors

6. 1. Introduction

Chronic infections with HBV and HCV are associated with serious health risks due to hepatic cirrhosis and hepatocellular carcinoma. Patients receiving maintenance HD therapy are at increased risk for acquiring these infections and have a higher prevalence of HBV and HCV than the general population (117, 118). Prior to effective screening of blood donations, HCV infection was associated with blood transfusions needed to correct the anaemia associated with kidney disease (257, 258) but patient to patient transmission in HD units is also reported (259, 260). HBV infection is usually due to patient to patient transmission within HD units (261). Recognition of the risk of nosocomial infection has resulted in recommendations that strict infection control procedures should be followed on HD units; patients with blood-bourne virus infections should be isolated from sero-negative patients during dialysis and patients as well as staff should be vaccinated against HBV (262, 263). The introduction of blood donor screening and a reduction in blood transfusions due to the availability of recombinant erythropoietin has significantly reduced the incidence of new HCV infections among HD patients in many countries (264-266).

Libya provides free access to maintenance HD for ESKD through a rapidly expanding network of centres. Although there are no national dialysis practice guidelines or infection control polices enforced by health care authorities, there is general agreement that patients on HD should be screened for HBV and HCV infection before the initiation of HD and monitored every 3-6 months thereafter (241). Sero-positive patients are dialysed on dedicated machines either in an isolated area or alongside sero-negative patients if space does not allow isolation (241). A national serological survey for HBV and HCV infections among the general population was performed in Libya during 2003 and revealed prevalences of 2.2% and 1.2%

for HBV and HCV, respectively (267). Other local surveys reported that the rate of HBsAg positivity among blood donors ranged from 1.3% to 4.6% (268), while the rate of HCV antibodies was 1.2% (269). Global data indicate that the prevalence of HBV and HCV infection is high in populations of Africa and the Middle Eastern regions (119-121). HCV infection was estimated by World Health Organisation to affect 4.6% of the Eastern Mediterranean population and 5.3% of the population of Africa (270). This study aimed to investigate for the first time the incidence and prevalence of HBV and HCV infection in the entire HD population of Libya.

6. 2. Methods

This descriptive study was carried out in all HD centres treating adult patients in Libya (n=39) from May 2009 to December 2010. One dialysis facility was excluded because it provided dialysis only to paediatric patients. Phase I of the study was a collection of cross-sectional data regarding all adult patients in maintenance HD facilities (n=2382). Large and medium capacity HD facilities were visited by the researchers in order to collect data. Patient records were used to obtain patients' age, gender, time on HD, medical history, sero-positivity to HBV and HCV as well as other laboratory results. Sero-positivity to HBV was defined by detection of HBsAg and sero-positivity to HCV by detection of anti-HCV antibodies by a third generation enzyme-linked immunosorbent assay (ELISA). ELISA tests were performed in local laboratories. In addition, 1732 patients from 24 centres were interviewed regarding other potential risk factors for HBV and HCV infection. These included history of blood transfusions and history of HD in another centre within Libya or abroad. Data was also obtained regarding infection control procedures at each HD facility. For small and remote facilities, data collection forms were posted to clinical supervisors who were requested to collect information about their patients. They were contacted frequently by phone to deal with any queries related to the required variables. Forms were returned within 30 days.

Phase II of the study was to prospectively detect sero-conversion to HBV or HCV in previously sero-negative HD patients during 1 year of follow-up. This step included a cohort of 1160 patients from 35 centres (four centres were excluded because of incomplete information).

All sero-conversions were recorded and included even if patient was transplanted or died afterwards. The research team frequently monitored HD patients during the year to assure the inclusion of every new sero-conversion. All new sero-conversions were retested to confirm the positive result. Field visits were repeated at the end of 1 year to validate the information.

Data are presented as mean±SD if normally distributed or median (interquartile range) if not. Analysis was performed using SPSS version 16.0. A Chi-square test was used to compare frequencies between groups. Correlations were tested with a Pearson's test. A t-test was used to compare means between groups for data with normal distribution or Mann-Whitney test for non-parametric data

Permission to conduct the study was granted from the ministry of health. The project was approved by the Libyan National Committee for Bioethics and Bio-safety. Patients gave written informed consent to be interviewed. The study was performed by a Libyan researcher with support from a Nephrology Department in the United Kingdom.

6. 3. Results

The median age of adult HD patients included was 49 years (range 36-61 years) and 58% were male. A total of 831 patients (34.9%) were sero-positive for HBV and/or HCV. The majority of infected patients were positive for anti-HCV antibodies (31.1%) and 2.6% were HBsAg positive. Twenty-eight patients (1.2%) had mixed infection with HBV and HCV (Table 6. 1). Of the sero-positive patients 4.7% were known to be infected before the initiation of HD. Overall the prevalence of sero-positivity was similar among males and females (35.8% versus 33.7%, respectively) but males comprised a greater proportion of those with HBV or combined infection (Table 6. 1; P=0.01 for comparison between groups).

Table 6.1: Frequency, age and gender distribution of HBV and/or HCV sero-positive haemodialysis patients. Data are number (percent) or median (interquartile range)

		HBV n=62	HCV n=741	HBV+HCV n=28	Total n=831
Frequency	Male	45 (72.6%)	427 (57.6%)	22 (78.6%)	494 (59%)
	Female	17 (27.4%)	314 (42.4%)	6 (21.4%)	337 (41%)
Age (years)	Male	49 (33-58)	46 (36-59)	40 (31-45)	46 (36-59)
	Female	44 (33-61)	48 (34-59)	44 (42-54)	47 (35-59)

The prevalence of HBV and/or HCV infection varied widely between HD centres from 0% to 75.9%. Four centres had no sero-positive patients and half of centres were free from HBV infection. Patients' sero-positive for both viruses were found in 28.2% of centres (figure 6.1).

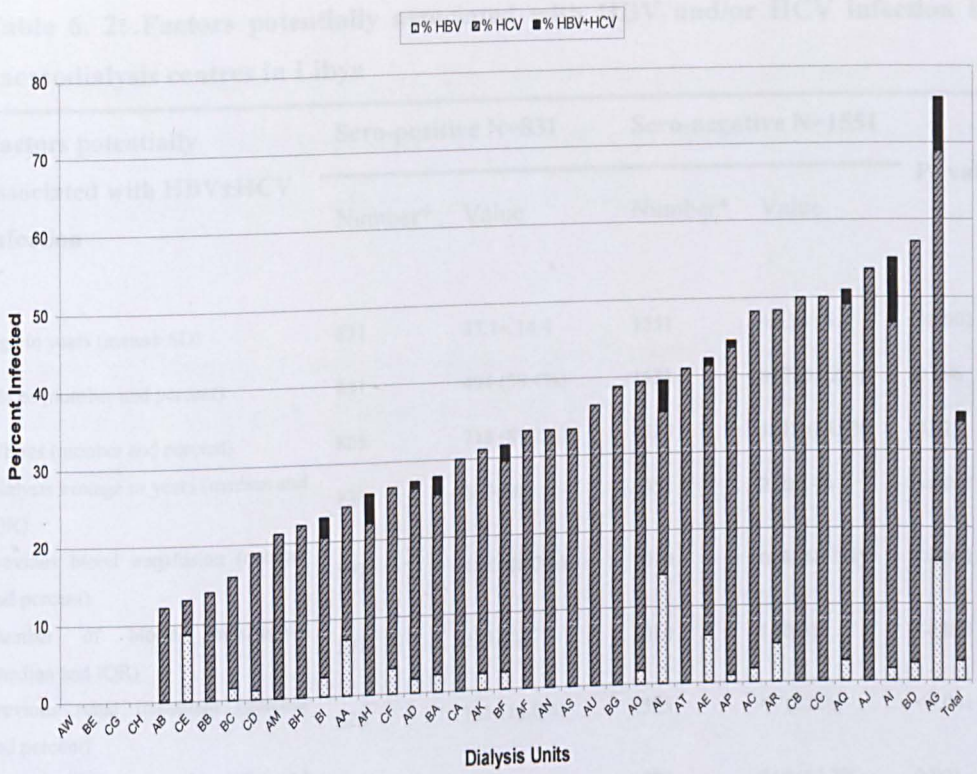

Figure 6. 1: Prevalence of HBV and/or HCV sero-positivity in different haemodialysis centres in Libya

Univariate analysis of potential risk factors for infection with HBV and/or HCV was performed by comparing infected and non-infected patients (Table 6. 2). Sero-positive patients were younger and had been receiving dialysis for substantially longer. History and number of blood transfusions was also significantly associated with sero-positivity. Mean values for alanine aminotransferase and aspartate aminotransferase were higher in sero-positive patients despite being within the normal range.

Table 6. 2: Factors potentially associated with HBV and/or HCV infection in haemodialysis centres in Libya

Factors potentially associated with HBV±HCV infection	Sero-positive N=831		Sero-negative N=1551		P- value
	Number*	Value	Number*	Value	
Age in years (mean± SD)	831	47.1± 14.4	1551	49.5± 16.2	<0.001
Males (number and percent)	831	494 (59.4%)	1551	887 (57.2%)	0.296
Whites (number and percent)	805	718 (89.2%)	1528	1312 (85.9%)	0.023
Dialysis vintage in years (median and IQR)	831	6 (3-10)	1551	2 (0.1-3)	<0.001
Previous blood transfusion (number and percent)	597	482 (80.7%)	1010	688 (68.1%)	<0.001
Number of blood transfusions (median and IQR)	597	2 (1-3)	1010	1 (0-3)	<0.001
Previous renal transplant (number and percent)	822	115 (14.0%)	1533	41 (2.7%)	<0.001
Previous dialysis abroad (number and percent)	617	376 (60.9%)	1025	540 (52.7%)	0.001
Previous dialysis in another Libyan centre (number and percent)	612	324 (52.9%)	1018	447 (43.9%)	<0.001
Haemoglobin level in g/dl (mean± SD)	831	10.2± 1.9	1551	9.7± 1.8	<0.001
Alanine Aminotransferase in IU/L (mean± SD)	269	27.8± 20.2	353	19.6± 17.9	<0.001
Aspartate Aminotransferase in IU/L (mean± SD)	232	29.6±21.1	328	21.3±20.3	<0.001
Diabetes (number and percent)	831	195 (23.5%)	1551	551 (35.5%)	<0.001
Erythropoietin treatment (number and percent)	604	450 (74.5%)	1059	830 (78.4%)	0.071

*Number of patients with valid data for each variable
IQR: interquartile range

Results of the prospective study showed that 89 of 1160 (7.7%) previously sero-negative patients sero-converted during 1 year. The majority (82 patients) developed anti-HCV antibodies (incidence 7.1%). Seven patients became positive for HBsAg (incidence 0.6%). Age and gender distribution of those who sero-converted is shown in Table 6. 3.

Table 6. 3: Frequency, age and gender distribution of patients who sero-converted during 1 year of follow-up. Data are number (percent) or median (interquartile range)

		HBV	HCV	Total
		n=7	n=82	n=89
Frequency	Male	5 (71.4%)	49 (59.8%)	54 (61%)
	Female	2 (28.6%)	33 (40.2%)	35 (39%)
Age (years)	Male	50 (35-67)	50 (38-64)	50 (38-64)
	Female	57 (40-73)	52 (44-64)	52 (43-65)

Figure 6. 2. shows wide variation in rates of newly acquired infections between different dialysis centres. No sero-conversion was found in two small-capacity centres (one treating 2 patients and the other, 5 patients). New HBsAg positive cases were detected in 4 centres in 3.3-10.3% of previously negative patients. All new HBV cases were referred from centres already treating HBV infected patients. New HCV infections were reported in most centres (33 of 35) but the rate of HCV sero-conversion varied widely from 1.5% to 31% of patients. Most of the centres with HCV sero-conversions (31/33) were providing HD treatment to previously HCV-infected patients. However, anti-HCV antibodies were discovered in 9 patients (31%) in a centre which was previously treating exclusively sero-negative patients (coded CG). Two other HCV sero-conversions occurred in another previously sero-negative HD centre (coded BE).

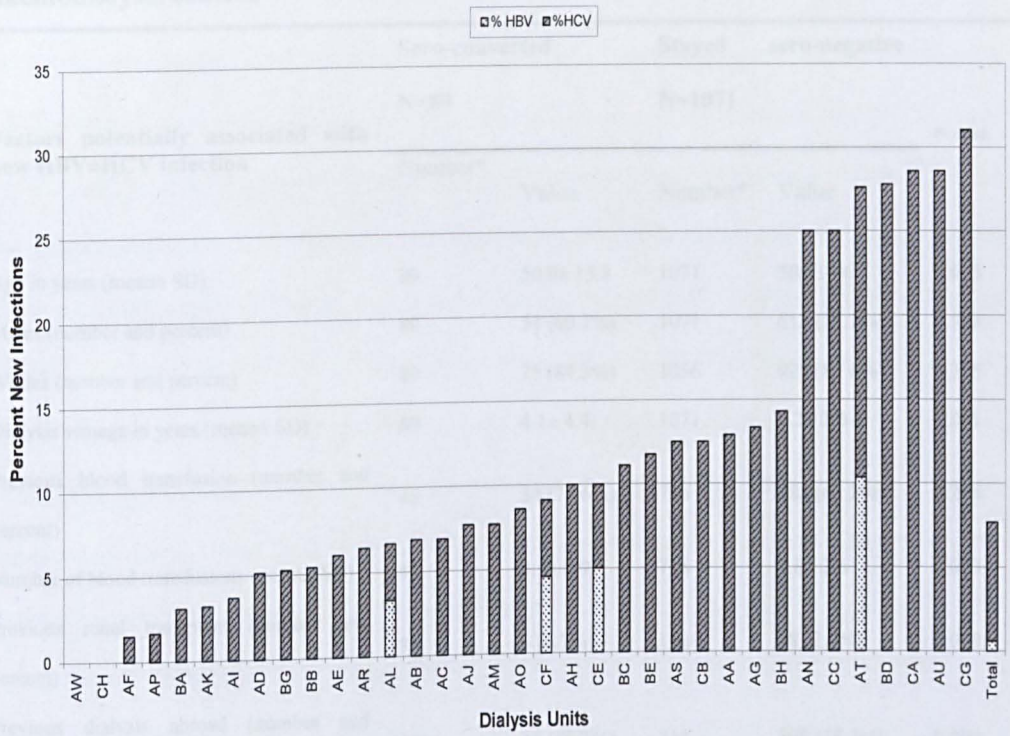

Figure 6. 2: Incidence of new HBV or HCV infections in haemodialysis patients during a 1-year follow up period

There were no correlations between number of HD patients treated in each centre and the prevalence or incidence of sero-positivity to HBV or HCV. There was no difference in prevalence or incidence of HBV or HCV infection between units that: routinely practiced isolation of sero-positive patients versus those that did not; units with hand washing facilities in each cubicle versus not and units that had adequate facilities for sharps disposal versus not.

Analysis of possible risk factors for new HBV or HCV infections is shown in Table 4. Only duration of dialysis, history of previous renal transplant and history of receiving HD in another centre in Libya were significantly different between patients who sero-converted and those who remained sero-negative.

Table 6. 4: Factors potentially associated with new HBV or HCV infection in haemodialysis centres

Factors potentially associated with new HBV±HCV infection	Sero-converted N=89		Stayed sero-negative N=1071		P- value
	Number*	Value	Number*	Value	
Age in years (mean± SD)	89	50.9± 15.8	1071	50± 16.6	0.635
Males (number and percent)	89	54 (60.7%)	1071	613 (57.2%)	0.528
Whites (number and percent)	89	75 (84.3%)	1056	927 (87.8%)	0.335
Dialysis vintage in years (mean± SD)	89	4.1± 4.4	1071	2.2± 2.6	0.001
Previous blood transfusion (number and percent)	45	34 (75.6%)	716	481 (67.2%)	0.244
Number of blood transfusions (mean± SD)	45	3.6± 6.9	716	1.8± 2.6	0.083
Previous renal transplant (number and percent)	89	6 (6.7%)	1064	28 (2.6%)	0.028
Previous dialysis abroad (number and percent)	48	27 (56.3%)	714	395 (55.3%)	0.900
Previous dialysis in another Libyan centre (number and percent)	48	31 (64.6%)	707	371(52.5%)	0.023
Haemoglobin level in g/dl (mean± SD)	89	9.9± 2.1	1071	9.6± 1.8	0.220
Alanine Aminotransferase in IU/L (mean± SD)	27	21.9± 22.7	274	18.6± 17.8	0.272
Aspartate Aminotransferase in IU/L (mean± SD)	24	23± 23.8	252	20.8± 21.2	0.925
Diabetes (number and percent)	89	35 (39.3%)	1071	385 (35.9%)	0.524
Erythropoietin treatment (number and percent)	51	7 (13.7%)	729	100 (13.7%)	0.999

*Number of patients with valid data for each variable

6. 4. Discussion

The prevalence of anti-HCV antibodies in patients receiving HD (31.1%) was remarkably high and is approximately 25 times higher than in the general population (267). It is also higher than the prevalence of 20.5% reported by Daw et al in a sample of 200 HD patients in 2001 in Libya (269). Globally the prevalence of HCV among patients receiving HD varies from as low as

6.1% in Germany (126) to as high as 76% in Casablanca (127). In general, North Africa and the Middle East are high prevalence areas both in the general population and in HD patients (270). Previous studies from the region have reported a prevalence of anti-HCV antibodies in HD patients of 50% in Saudi Arabia (128), 42% in Tunisia (129), 20.2% in Turkey (130) and 21% in Jordan (20). In contrast, the observed prevalence of HBV infection (2.6%) is similar to the general population and similar to that reported in HD patients in other regions including Europe (4.1%), Japan (2.2%) and the United States (2.4%) (247). A study sample from the DOPPS that included 8615 adult HD patients from 308 dialysis facilities in Western Europe and the United States, reported prevalence rates for HBV infection ranging from 0% to 6.6% (122). Studies from less developed countries estimated that the proportion of HBsAg carriers in the HD population varies from 2% to 20% (271-274). According to the 2008 Saudi Centre for Organ Transplantation report, HBV sero-positivity was 4.6% in the Saudi HD population (19) while among Jordanian HD patients it was 5.9% (125). In general, the prevalence and incidence of HBV and HCV infections in HD patients reflects the prevalence of these infections in the general population, the quality of healthcare services in a community and the standards of infection control practices in HD units. The importance of HBV and HCV as a health risk in patients on HD is illustrated by our observation that 3% of deaths in Libyan HD patients during a 1 year observation period were due to liver failure and that 13 of the 14 patients who died of liver failure were sero-positive for HCV and/or HBV.

Our data show that sero-positive patients were significantly younger on average than sero-negative patients. This observation is in agreement with a previous report from Libya showing that the highest prevalence of HCV antibodies was observed in HD patients aged 36-55 years (269). Other studies (122, 275, 276) have reported a higher prevalence of HBV or HCV sero-positivity in older patients and the reason for this difference in not clear. On the other hand, the prevalence and incidence of HBV or HCV sero-positivity was significantly related to the length of time on HD. This is consistent with nosocomial transmission related to dialysis since longer duration of dialysis represents a longer period at risk of acquiring an infection. Similar observations have been reported by other authors (131-134). Prevention of nosocomial transmission is of vital importance in Libya as HCV antiviral treatment is expensive and its availability is limited to only a few centres.

A positive history of blood transfusions as well as the number of blood transfusions was strongly associated with HBV or HCV infection at baseline, but not with new infections. Prior to the introduction of effective screening of blood donors, blood transfusions were recognised as the leading source of HCV infection and some of these infections may have been acquired before adequate screening was introduced (126, 131). In addition it is possible that some blood donors with HCV infection are being missed by current screening procedures and these may need to be reassessed (277, 278). On the other hand the lack of association between blood transfusions and new infections suggests that fewer infections are acquired by this route than previously. A large proportion of patients had previously received blood transfusions. The risk of infection could therefore be further reduced by more effective management of anaemia with iron supplementation and erythropoietin. In accordance with other studies (134-136), HBV or HCV infection was more prevalent in patients with a history of previous renal transplant. Infection in these patients might have been transmitted from an infected donor kidney or blood transfused peri-operatively. This observation emphasizes the need for adequate screening of potential kidney donors, which is deficient in some countries. The shortage of donated kidneys in Libya induces many patients to seek a transplant abroad.

Another concern raised by the current study is that HBV or HCV infection was associated with a history of HD in another centre either in Libya or abroad. Many patients travel for social reasons but some also transfer to a maintenance HD centre after initiating dialysis as an emergency in a specialised centre providing acute services or may travel to another centre for surgery to create an AVF (241). The association of hepatitis virus infection with travel suggests that the risk of nosocomial infection varies between dialysis centres within Libya and abroad. The former is confirmed by our data showing a marked variation in both prevalence and incidence of HBV and HCV infection among Libyan HD units (figures 1 and 2). These observations emphasize the importance of isolating patients following their return and monitoring them for sero-conversion.

Prospective follow up of sero-negative HD patients enabled us to verify 89 sero-conversions for HBV or HCV during 1 year, giving an overall incidence of 7.7% for new infections. The incidence rate of 0.6% for HBsAg sero-conversion is similar to that reported in Europe, Japan and the United States (0.4-1.8 per 100 patient-years) (122). Three new HBsAg positive patients

were detected in a single centre that was treating 20 other HBsAg positive patients and 2 new cases were detected in another centre that was treating 14 HBsAg positive patients, suggesting that nosocomial transmission probably occurred. We observed a high incidence of new HCV infections during the 1-year observation period (7.2%). The reported incidence of new HCV infections varies considerably between countries. A rate as low as 0.4% was observed in France from 1997 to 2000 (279) but higher rates have been reported from the Mediterranean region. According to the 2008 Saudi Centre for Organ Transplantation report, the annual rate of HCV sero-conversion in Saudi HD patients was 7-9% (19) while in Jordan it was 2.6% (20). In our study most new cases were observed in centres treating other patients with HCV infection, suggesting nosocomial transmission. Interestingly 9 new HCV infections were observed in one unit and 2 in another that previously accepted only patients without HCV infection. This raises the possibility of transmission from a carrier that was not detected by current screening procedures.

A striking observation from this study is the wide variation in incidence and prevalence of HBV and HCV infections among different HD units (figures 1 and 2). Interestingly none of the potential centre-related factors that we assessed formally explained this variation. On the other hand, we observed variations in other practices that may be relevant. Most facilities faced a problem of increasing number of patients and most of them responded by adding more HD stations at expense of space and staff. Infection control precautions also varied widely between centres. They were strictly enforced in some places but frequently breached in others. This seemed to depend on staff initiative rather than national guidelines. On the other hand, dialyser reuse was not permitted and all bloodlines as well as other consumables were disposed after a single use (241). Some brands of HD machines were equipped with a sphygmomanometer. Otherwise, most non- disposable instruments used in HD environment were shared between sero-positive and sero-negative patients. The use of multi-dose vials of heparin was common and is likely to have been an important cause of nosocomial infections. Many patients started HD without being vaccinated against HBV. Even in vaccinated patients the antibody titre was not assessed. The wide variation in HBV and HCV prevalence and incidence between dialysis centres implies that there is potential to reduce blood-borne virus infection by transferring best practice from HD centres with low infection rates. In particular infection control procedures

should be investigated in centres with high infection rates and the use of multidose heparin vials must be stopped urgently. Previous studies from the region show that with appropriate intervention HCV infection rates in HD centres may be substantially improved. For example in Iran, HCV prevalence reduced from 14.4% in 1999 to 4.5% in 2006 (280) and in Saudi Arabia from 2.4% in 2001 to 0.2% in 2005 (281).

Several limitations of this study should be conceded. Medical records were often incomplete and additional clinical information was frequently obtained by interviewing staff and patients. Serological testing was done in local laboratories and it is likely that there was some variation in the quality of testing. Testing for HCV relied on a third generation ELISA to detect anti-HCV antibodies and confirmation or genotyping by polymerase chain reaction (PCR) is currently not available in most centres.

6. 5. Conclusion

Patients on maintenance HD in Libya have a high incidence and prevalence of HCV infection and lower rates of HBV infection. The factors associated with HBV and HCV infection are highly suggestive of nosocomial transmission within HD units. Urgent action is required to improve infection control measures in HD centres and to reduce dependence on blood transfusions for the treatment of anaemia. The data presented were obtained before the recent conflict in Libya. It is possible that disruption of services due to the conflict may have exacerbated the problem of hepatitis virus infection in HD patients.

Chapter 7

Results

Vascular access in patients receiving haemodialysis in Libya

7. Vascular access in patients receiving haemodialysis in Libya

7. 1. Introduction

Creating and maintaining an adequate vascular access in patients receiving HD remains a major challenge facing dialysis providers worldwide. A native AVF represents the optimal form of vascular access because it affords superior blood flow as well as lower morbidity and mortality as compared to CVC (89, 91, 282-285). The updated NKF/KDOQI guidelines have strongly recommended the use of AVFs as the vascular access of first choice for HD or AVGs if a native AVF cannot be achieved to limit the use of CVCs to a minimum (93). Initiation of HD with an AVF is associated with improved survival but this is often difficult to achieve because it depends on multiple factors including adequate preparation time at pre-dialysis follow up (149, 286), availability of surgeons with the necessary competencies and adequate facilities for performing the surgery (149, 287, 288). Several patient factors also affect the success rates of vascular access surgery including age, gender, diabetes, peripheral vascular diseases and obesity (91, 149, 289-291). Thus the pattern of vascular access use varies widely in different HD populations. A high prevalence of AVF utilisation is reported in Europe (10) and Australia (93) whereas it was as low as approximately 30% in the United States during 1990s but rose to 47% by 2007 in part due to the "Fistula First Breakthrough Initiatives" (4, 285, 292). A second challenge to maintaining a high prevalence of permanent vascular access is loss of AVF or AVG due to dysfunction. Many patients require more than one AVF during their time on HD treatment and rates of intervention vary between different HD populations. Dysfunction occurs due to thrombosis, infection, aneurysm formation and/or haemorrhage.

Dialysis has been provided universally in Libya for about four decades through an expanding network of centres (n=39), almost exclusively as HD (241). The prevalence rate of ESKD treated by dialysis in Libya is among the highest in the Middle East region (624 pmp) (241). Services for creation of AVF are, however, limited to only a few centres (15%) (241),

providing a significant challenge to achieving high rates of AVF use. Pre dialysis care is very limited because of weak PHC and a shortage of nephrologists (241). Although all HD facilities are run by the Ministry of Health, there is a lack of national guidelines to facilitate uniform practice and promote efforts to improve services for the creation of AVF. There are no data available regarding the patterns of vascular access utilisation in Libya or risk factors associated with failure of permanent vascular access. We therefore aimed to conduct the first comprehensive study of vascular access utilisation in HD patients in Libya.

7. 2. Methods

A prospective observational study was undertaken of all adult (age 16 years or more) patients receiving HD treatment in 25 HD facilities (out of 39) in Libya from May 2009 to December 2010. In Phase I we performed a cross-sectional study of 1712 patients (72% of total national HD population; n=2383). Patients who were away at the time of the field visit were excluded. Each HD facility was visited by the researchers and data regarding demographics, dialysis treatment and mean predialysis blood pressure readings from the last 3 HD sessions were collected. Data regarding vascular access utilisation and complications related to vascular access were collected mainly through interviews with patients. Other information including weight, height, blood pressure and haemoglobin values were collected from medical records and dialysis staff.

In the second phase of the study patients who were using permanent vascular access in phase I were interviewed again after a minimum of 1 year. Data were not available for 142 patients due to loss to follow-up, transfer to a non-participating dialysis unit or patient refusal. Patients were asked about any incidents of vascular access related complications (thrombosis, infection and haemorrhage) and hospitalisation. All vascular access related incidents were recorded and included in the study even if the patient was transplanted or died afterwards.

Ethical approval was granted for the research from the Ministry of Health. The project was approved by the Libyan National Committee for Bioethics and Bio-safety. Participants gave written informed consent.

Continuous variables are presented as median and interquartile range and groups were compared using a Mann-Whitney test. Categorical variables were compared using a Chi-square test. Data analysis was performed by using SPSS version 16.0. A p-value of <0.05 was regarded as significant.

7. 3. Results

At baseline the majority of patients (91.9%; n=1573) were using permanent vascular access (AVF or AVG) for maintenance HD. Of these, 76 patients were using an AVG (4.4% of the total HD population). Patient characteristics are summarised in Table 7. 1. Patients with AVF were more likely to be male and less likely to be diabetic that those with CVCs. Notably the median dialysis vintage was 10-fold higher in those with permanent vascular access. Patients with AVF had lower pre-dialysis blood pressure and higher haemoglobin than those with CVCs. The use of tunnelled catheters was limited to very few patients, most of them female and over half diabetic.

Table 7. 1: Patient characteristics by vascular access type

Characteristics	Types of Vascular Access				
	Permanent Vascular Access n=1573 (91.9)		CVC N=120 (7.1)	Tunnelled Catheter N=19 (1.1)	Total N=1712
	AVF N=1497 (87.4)	AVG N=76 (4.4)			
Age (years)	49 (36-61)	50 (36-61)	52 (37-64)	44 (26-62)	49 (36-61)
Male	869 (58)	40 (52.6)	69 (57.5)	7 (36.8)	985 (57.5)
Female	628 (42)	36 (47.4)	51 (42.5)	12 (63.2)	727 (42.5)
Duration of dialysis (years)	3 (1-7)	4 (2-7)	0.3 (0.1-0.7)	3 (1-7)	3 (1-6)
White ethnicity	1304 (89.6)	66 (86.8)	100 (84)	16 (84.2)	1486 (89)
Black ethnicity	151 (10.4)	10 (13.2)	19 (16)	3 (15.8)	183 (11)
Current smoker	189 (13.4)	10 (13.3)	7 (6.5)	1 (5.3)	207 (12.9)
Diabetic	440 (29.4)	28 (36.8)	55 (45.8)	10 (52.6)	533 (31.1)
Predialysis systolic blood pressure (mmHg)	145 (130-170)	160 (135-173)	150 (130-175)	160 (130-170)	150 (130-170)
Predialysis diastolic blood pressure (mmHg)	81 (80-90)	90 (80-90)	90 (80-100)	85 (70-90)	85 (80-90)
Body Mass Index in Kg/m^2	24.1 (21.3-27.5)	23.3 (20.7-29.5)	24.1 (21.3-27.7)	20.8 (20.2-28.4)	24.1 (21.2-27.6)
Haemoglobin (g/dl)	10 (8.8-11.4)	9.8 (8.8-11.3)	8.6 (7.6-9.6)	10 (8-11.5)	9.9 (8.7-11.3)

Data are median (interquartile range) or number (%)
AVF= Arteriovenous fistula
AVG= Arteriovenous graft
CVC = central venous catheter (non-tunnelled)

Upper arm permanent vascular access was more common than forearm overall but forearm vascular access was more common in males (<0.001). (figure 7. 1).

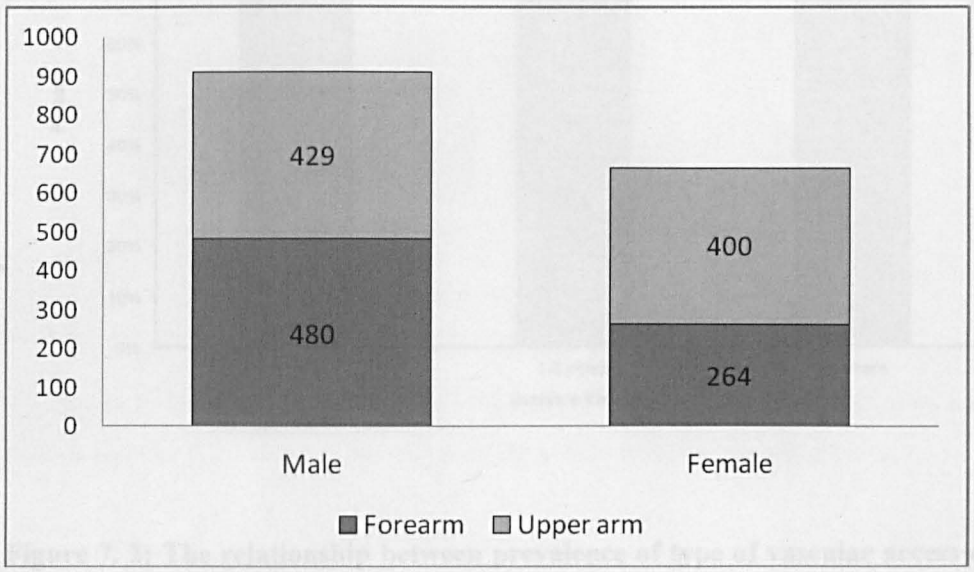

Figure 7. 1: Site of permanent vascular access according to gender

Utilisation of vascular access at the start of dialysis showed a strikingly different pattern. Most patients had commenced HD using a temporary CVC (91.8%) and only a small minority with an AVF (7.8%) or AVG (0.4%). None had started HD with a tunnelled catheter. Overall, 1448 patients were admitted to hospital at the time of initiation of HD (87.1%). Figure 7. 2 describes the relationship between the type of vascular access used and duration of HD. Utilisation of AVF for HD increased progressively in those who passed the first year of HD treatment.

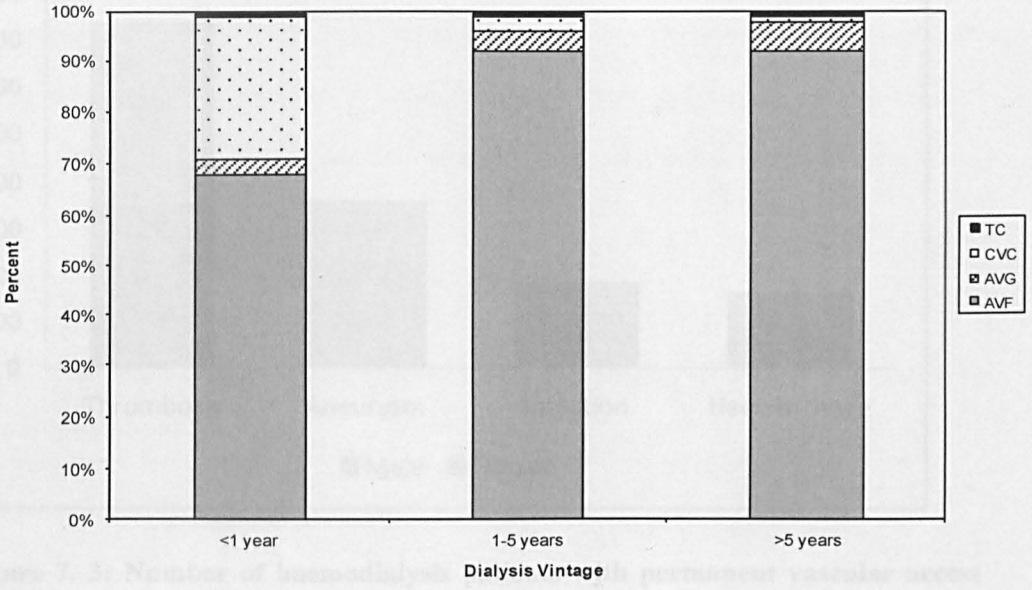

Figure 7. 2: The relationship between prevalence of type of vascular access used and dialysis vintage

(TC=tunnelled catheter; CVC=temporary central venous catheter; AVG=arteriovenous graft; AVF=arteriovenous fistula)

The most common vascular access- related complication was thrombosis and this was reported by almost half of patients (46.7%). Moderate to large aneurysm transformation was observed in 22.6% and was more common in males (P=0.003). History of infection was reported by 11.5% while moderate to severe haemorrhage was reported by 10.2%. (figure 7. 3).

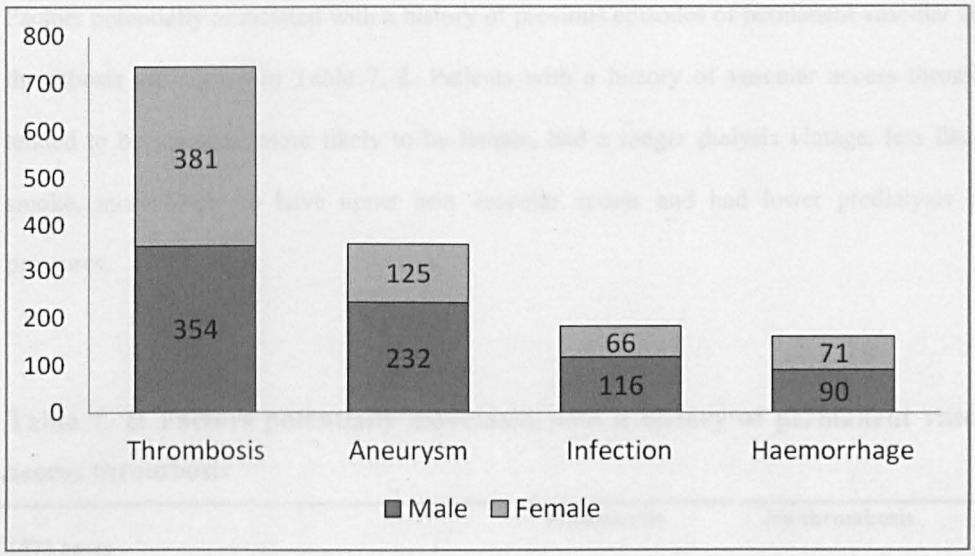

Figure 7. 3: Number of haemodialysis patients with permanent vascular access with a history of various types of vascular access related complications

Of those reporting thrombosis, it had occurred once in 57.8%, twice in 24.6% and three or more times in 17.6%. (figure 7. 4).

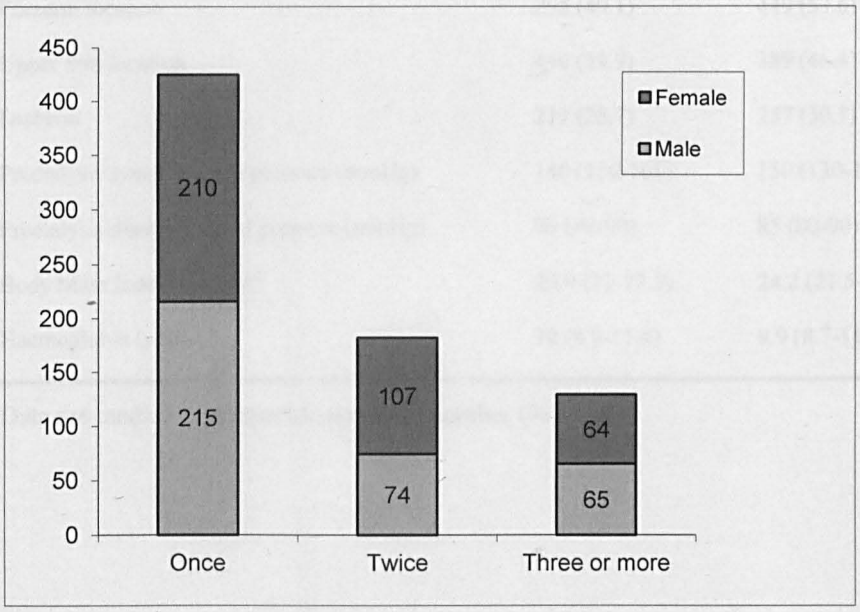

Figure 7. 4: Frequency of previous thrombosis of permanent vascular access in haemodialysis patients

Factors potentially associated with a history of previous episodes of permanent vascular access thrombosis are shown in Table 7. 2. Patients with a history of vascular access thrombosis tended to be younger, more likely to be female, had a longer dialysis vintage, less likely to smoke, more likely to have upper arm vascular access and had lower predialysis blood pressures.

Table 7. 2: Factors potentially associated with a history of permanent vascular access thrombosis

1573 cases	**Thrombosis** N=735 (46.7%)	**No thrombosis** N= 838 (53.3%)
Age (years)	46 (35-60)	50 (37-61)
Male	354 (48.2)	555 (66.2)
Female	381 (51.8)	283 (33.8)
Duration of dialysis (years)	5 (2-9)	2 (1-4)
White ethnicity	636 (89)	734 (89.6)
Black ethnicity	76 (11)	85 (10.4)
Current smoker	77 (11.1)	122 (15.4)
Forearm location	295 (40.1)	449 (53.6)
Upper arm location	440 (59.9)	389 (46.4)
Diabetic	211 (28.7)	257 (30.7)
Predialysis systolic blood pressure (mmHg)	140 (130-161)	150 (130-170)
Predialysis diastolic blood pressure (mmHg)	80 (80-90)	85 (80-90)
Body Mass Index in Kg/m^2	23.9 (21-27.5)	24.2 (21.5-27.6)
Haemoglobin (g/dl)	10 (8.9-11.4)	9.9 (8.7-11.4)

Data are median (interquartile range) or number (%)

Of patients with permanent vascular access, 24.4% reported an admission to hospital due to vascular access related complications during the year prior to interview. The proportion of female patients who reported hospitalisation was greater than males (28.8% vs. 21.3%; $p<0.001$).

Of those with permanent vascular access at baseline (n=1573), 142 were lost to follow-up. Thus 1431 (78.3%) were interviewed for a second time. Of these, 14.7% reported vascular access thrombosis during the one year study period. Thrombosis with infection was reported by 4.9% and thrombosis after moderate to severe haemorrhage was reported by 2.2%. Thrombosis was more common in female patients (18.1% vs. 12.3%; p=0.001). Hospitalisation for vascular access related complications was reported by 31.4%. Factors potentially associated with incident vascular access thrombosis in 1-year follow up period are shown in Table 7. 3. Those who developed thrombosis were more likely to be female or diabetic, have upper arm vascular access and lower predialysis blood pressures.

Table 7. 3: Factors potentially associated with incidence of permanent vascular access thrombosis (1-year follow up)

1431 cases	Thrombosis N=211 (14.7)	No thrombosis N= 1220 (85.3)	P value
Age (years)	49 (35-62)	48 (36-61)	0.996
Male	102 (48.3)	728 (59.7)	0.001
Female	109 (51.7)	492 (40.3)	
Duration of dialysis (years)	3 (1-7)	3 (1-7)	0.743
White ethnicity	183 (90.1)	1059 (88.8)	0.341
Black ethnicity	27 (11.4)	133 (11.2)	
Current smoker	20 (10.8)	168 (14.4)	0.111
Forearm location	88 (41.7)	593 (48.6)	0.037
Upper arm location	123 (58.3)	627 (51.4)	
Diabetic	86 (40.8)	361 (29.6)	0.001
Predialysis systolic blood pressure (mmHg)	140 (115-160)	150 (130-170)	<0.001
Predialysis diastolic blood pressure (mmHg)	80 (70-90)	89 (80-90)	<0.001
Body Mass Index in Kg/m^2	23.6 (20.7-27.9)	24.2 (21.3-27.7)	0.486
Haemoglobin (g/dl)	9.6 (8.7-10.9)	10 (8.8-11.4)	0.060

Data are median (interquartile range) or number (%)

7. 4. Discussion

The majority of patients (91.8%) in our study had started their HD therapy by using a temporary CVC. This is undesirable because CVCs are associated with several serious complications including inadequate blood flow, infection and central vein stenosis. Previous studies have found that late referral to a nephrologist is a major determinant of CVC use at initiation of HD and is associated with poorer outcomes. The use of CVCs at the initiation of HD varies in different countries. In the United States almost two thirds of patients initiate HD with a temporary CVC but lower rates were reported in Germany and Japan. In Egypt, only 10.2% of patients had a fistula created before the start of dialysis and a temporary CVC prior to

permanent access was used in 90% of patients (288). A report from a single dialysis unit in Casablanca showed that a temporary CVC was used to initiate HD in 86.3% (287). The high rate of temporary CVC use at the start of HD observed in our study reflects poor predialysis preparation and failure of the health care system to detect CKD before it reaches end-stage. Achieving a placement of permanent vascular access prior to initiation of HD in Libya will require improved screening programmes for CKD and the establishment of comprehensive primary care services as well as improved nephrology and surgical services.

Despite the obstacles to achieving permanent vascular access in Libya, the majority of prevalent HD patients studied (91.9%) had a functioning AVF or AVG. Data from DOPPS III (2005–2007) from 11 countries showed wide variation in vascular access patterns among countries with a highest rate of AVF (91%) in Japan and a lowest rate of AVF (47%) in the United States. The high rate of permanent vascular access use in Libya likely reflects an element of selection since patients who are unable to obtain permanent vascular access are less likely to survive. Our observation that patients with permanent vascular access had a dialysis duration 10-fold that of patients with a CVC supports this conclusion but further prospective research is required to investigate outcomes among those initiating HD with a CVC in Libya. On the other hand, the high utilisation of permanent vascular access reflects determination on the part of dialysis staff and patients to overcome considerable obstacles to achieve AVF or AVG formation, since the necessary surgical services are available in only 15% of centres (241). There is an urgent need to improve surgical services so that permanent vascular access can be more readily offered to all patients. Access to tunnelled dialysis catheters in extremely limited in Libya and they are therefore used by only a small minority.

Patterns of complications related to permanent vascular access are similar to those reported from other countries, with thrombosis the most frequent. Gender differences in site and patency rates of permanent vascular access have been reported by several studies (31, 32, 91, 293, 294) and, similar to our study, many authors have observed that females are less likely than males to have their permanent vascular access placed in the forearm because they have smaller vessels than men (31, 37). Allon et al. reported that women were significantly less likely to have suitable vessels for construction of AVF, when objective preoperative sonographic criteria were used (37). Gender discrepancy was also reported by Miller et al. who reported that

successful AVF formation was less likely be achieved in women despite routine preoperative mapping and frequent interventions to salvage AVF that failed to develop (295).

Diabetes has been identified as a risk factor for reduced utilization of AVF in affected patients (91, 148, 149, 288, 296). The health care financing adminstration in the United States reported that only 22% of diabetic patients receiving HD were using AVF, as compared with 30% of non-diabetic patients (297). There is controversy as to whether diabetes is an independent risk factor for reduced AVF use or is a marker for associated factors such as arteriosclerosis (298). Leapman et al. observed excess poor outcomes with AVF in elderly and diabetic patients and recommended that other vascular access devices be considered for these patients (299). Diabetes was found to have an association with cephalic arch stenosis which contributes to thrombosis (300). These observations are important because diabetes is the single most common cause of ESKD in many countries including Libya. Improved surveillance of fistula function in patients with diabetes may help to preserve vascular access function in this important subgroup.

Our study revealed a remarkably high rate of hospitalisation related to vascular access. First, most patients had commenced HD using a temporary CVC and most were hospitalised at the time of initiation of HD. Second, a quarter of HD patients with permanent vascular access as baseline reported a history of admission to hospital due to permanent vascular access related complications during the year preceding the interview. Third, during one year follow up approximately one third of HD patients were admitted to hospital with permanent vascular access related complications. Hospitalisation rates for vascular access related problems are also high in the United States (60, 87, 301). A report by the USRDS (2011) shows that admissions for vascular access related infection have fallen from 2005 to 2009 by 19 % while admissions for sepsis remained high at 108 per 1,000 patient years in 2009 (10). Thus improved provision and maintenance of vascular access could result in considerable reductions in hospitalisations with improved quality of life for patients and reduced cost to the healthcare system.

Several limitations to our study should be conceded. The type and frequency of vascular access related complications were obtained mainly from patient histories because most of the vascular

access related complications were not documented in the medical records. Among prevalent patients dialysis vintage varied widely and there was an element of selection bias since only surviving patients could be included. One hundred and forty two patients were lost to follow up during the 12 month observation period and our data may therefore underestimate the incidence of vascular access related complications in the study population.

7. 5. Conclusion

Few patients in Libya initiate HD using a permanent vascular access, but most achieve it thereafter. Attempts to improve the predialysis preparation including creation of definitive vascular access will likely result in improved outcomes and reduce the need for admission to hospital. This will require improved provision of primary care as well as nephrology and surgical services. Monitoring of vascular access to identify those at risk of complications could improve longevity of vascular access and should initially be targeted at females and patients with diabetes. This research was conducted prior to the recent conflict in Libya, which likely has resulted in disruption of nephrology and surgical services. Re-establishment of these services and improved provision of definitive vascular access at more centres should be made a priority in the rebuilding of healthcare in Libya.

Chapter 8

Results

Determinants of survival in patients receiving dialysis in Libya

8. Determinants of survival in patients receiving dialysis in Libya

8.1. Introduction

Maintenance dialysis sustains life for more than one million patients throughout the world. Nevertheless survival on dialysis is dramatically reduced compared to the general population and is comparable to survival with many forms of cancer. Thus survival is arguably the most important outcome measure for assessing the overall quality of dialysis provision in a centre, region or nation. Previous studies have identified considerable variation in survival rates from different centres (39, 40, 302), influenced by the type of dialysis used (303, 304), demographic and social characteristics of dialysis patients (305, 306), provision of predialysis care and associated comorbidities such as diabetes, cardiovascular diseases, abnormal bone and mineral metabolism and malignancies (30, 40, 307). The observed variation also suggests that intervention is possible to improve survival. Practice guidelines have been developed to standardise the delivery of dialysis and promote best practice and have likely contributed to improvements in survival rates seen in Europe, Japan and the United States (308).

In Libya, free access to state-funded dialysis has been available for four decades but data regarding outcomes are scarce. A renal registry has not yet been established to collect outcome data and there are no nationally accepted clinical practice guidelines to promote best practice in dialysis care. We therefore aimed to investigate survival rates, determinants of survival and causes of death in Libya's dialysis population.

8. 2. Methods

This prospective observational cohort study included all patients treated at dialysis facilities in Libya (n=38/40) aged 16 years or more who had reached at least 90 days of dialysis during May 2009. One dialysis facility was excluded because it provided dialysis only to paediatric patients and another new facility because no patients had been treated for more than 90 days.

Large and medium capacity HD facilities were visited by the researchers in order to collect data. For small and remote facilities, data collection forms were posted to clinical supervisors who were requested to collect information about their patients. They were contacted frequently by phone to deal with any queries related to the required variables. Forms were returned within 30 days. On enrolment, data collected included socio-demographic information, dialysis modality, body weight, height, history of diabetes, type of primary renal disease, haemoglobin concentration, history of previous renal transplantation and date of dialysis initiation. In addition, 1759 patients from 26 centres were interviewed regarding other potential risk factors for mortality. These included modes of presentation with ESKD, clinical history, predialysis systolic and diastolic blood pressure, delivered HD hours per week and results of biochemical tests. Planned onset of dialysis was defined as a history of predialysis medical care for 3 months prior to the start of dialysis. Physical independency is defined as a normal physical performance without the need for aids or assistance.

Survival was assessed after one year of follow-up. The outcome of all participants was recorded except for patients who received a renal transplant, transferred to another dialysis unit where a follow up could not be determined or recovered renal function. Patients who changed to another dialysis modality were included. Cause of death was recorded from the medical records of patients and grouped into 10 categories. "Unknown" was used when the cause of death could not be identified.

Permission to conduct the study was granted by the Ministry of Health. Ethical approval for the research was obtained from the Libyan National Committee for Bioethics and Bio-safety. Patients each gave written informed consent.

Continuous variables are presented as mean± SD if normally distributed or median and interquartile range if not. Groups were compared using a *t*-test or Mann-Whitney test. Categorical variables were compared using chi-square test. Factors associated with mortality in the univariate analyses were included in a multivariable binary logistic regression analysis to identify independent risk factors for mortality. The exact date of death was not available in many patients and Cox regression models could therefore not be employed. Data analysis was performed by using SPSS version 16.0 (SPSS, Inc., Chicago, IL, United States). A p-value of <0.05 was regarded as significant.

8. 3. Results

A total of 2273 patients who had been on dialysis for at least 90 days in 38 dialysis centres were followed up for one year. The mean age was 48.7±15.5 years and 57.1% were males. The majority were receiving HD and only 26 were on PD (1.2%). Sixty-seven patients (3%) received a renal transplant and 46 patients were transferred to another dialysis unit where their follow up could not be confirmed. One patient recovered renal function after 2 years of HD. Thus 2159 patients were successfully followed up and included in the analysis of survival. At the end of the observation period the majority of patients (1697) were still receiving HD while only 4 patients had converted to PD. Four hundred and fifty eight patients died, giving a crude annual mortality rate of 21.2% (HD: 448 of 2133=21.0%; PD: 10 of 26=38.5%).

The highest mortality was observed in the age group 75-84 years (43.3%) whereas the best survival was in the age group 25-34 years (figure 8. 1). The causes of death are shown in figure 8. 2. By far the most common cause of death was cardiovascular disease (ischaemic heart disease 31%; cerebrovascular disease 16%) and infection was the second most common. The mortality rate in the Libya's 38 dialysis centres ranged from 0% to 70%. A particularly high mortality rate of over 30% was observed in 7 centres (figure 8. 3).

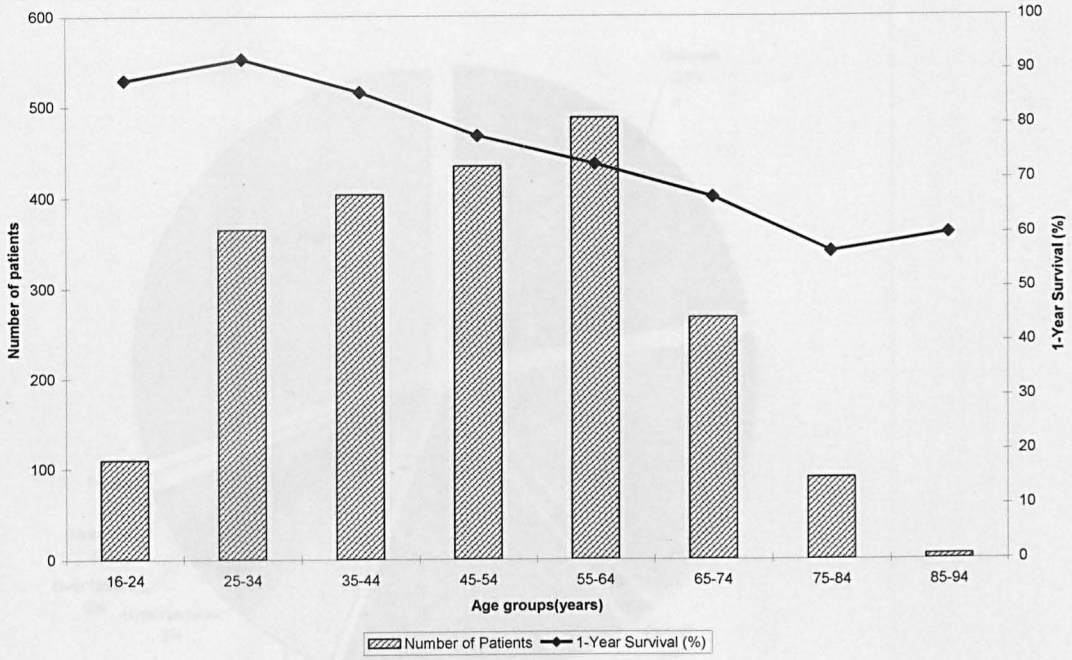

Figure 8. 1: 1-year survival (%) among patients who were alive after 90 days of dialysis and number of patients in each age group.

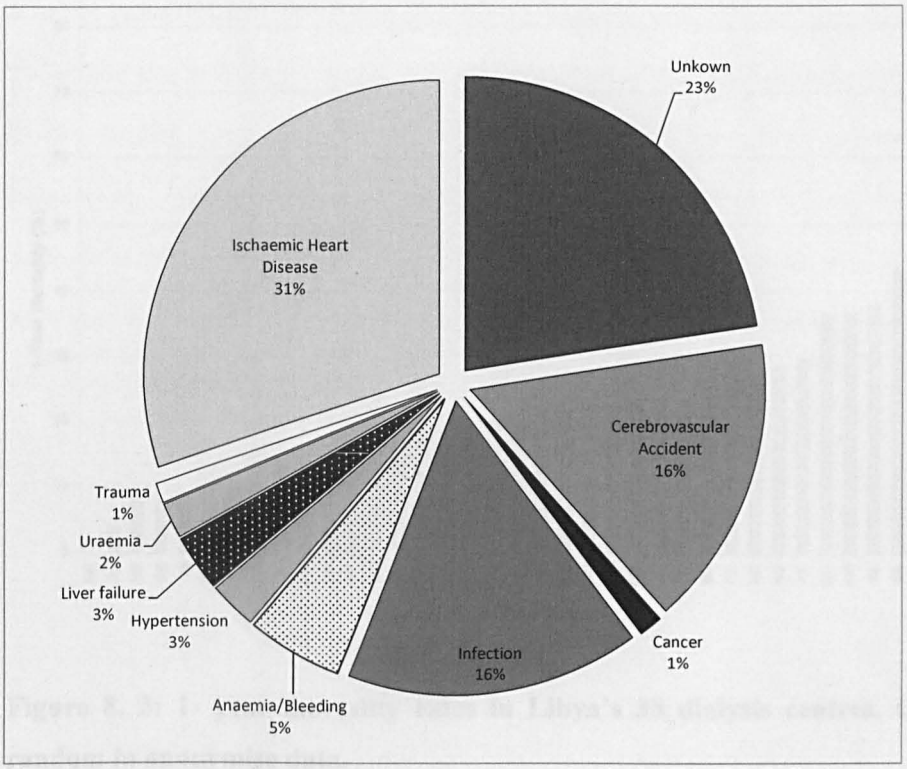

Figure 8. 2: Causes of 1- year mortality in dialysis patients in Libya's dialysis centres

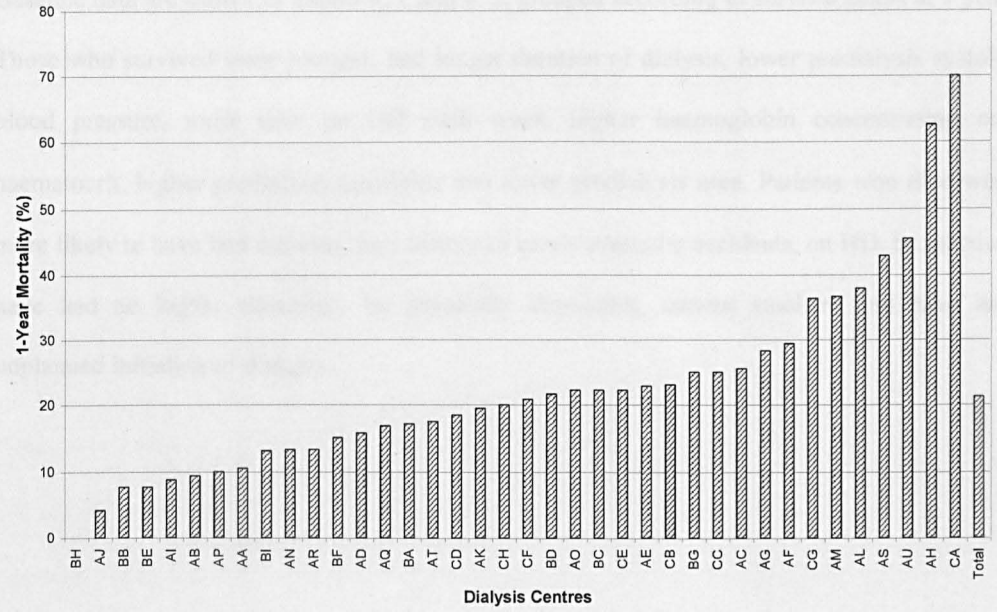

Figure 8. 3: 1- year mortality rates in Libya's 38 dialysis centres. Codes are random to anonymise data.

Baseline data are shown in Tables 8. 1 and 8. 2, grouped according to survival status at 1 year. Those who survived were younger, had longer duration of dialysis, lower predialysis systolic blood pressure, more time on HD each week, higher haemoglobin concentration and haematocrit, higher predialysis creatinine and lower predialysis urea. Patients who died were more likely to have had diabetes, past history of cerebrovascular accidents, on HD, be married, have had no higher education, be physically dependent, current smokers and have had unplanned initiation of dialysis.

Table 8. 1: Baseline data grouped according to survival status at 1 year. (Continuous variables)

2159	Outcome of dialysis patients				P-value
	Survived N=1701		Died N=458		
	Number*	Value	Number*	Value	
Age in years	1701	46 (34-59)	458	55.7 (46-66)	0.001
Age at onset in years	1701	41 (28-55)	458	54 (42-63)	0.001
Dialysis vintage in years	1701	3 (1-7)	458	2 (1-5)	0.001
Body Mass Index (kg/m^2)	1698	23.7 (20.8-27)	457	23.8 (21-27.6)	0.178
Predialysis systolic blood pressure	1213	140 (130-170)	338	150 (130-170)	0.002
Predialysis diastolic blood pressure	1213	85 (80-90)	338	85 (80-90)	0.300
Haemodialysis hours per week	1167	9.98±2.3	330	9.55±2.4	0.003
Serum Albumin (g/dl)	413	4.4 (3.9-5)	151	3.6 (2.3-4.5)	0.001
Haemoglobin level in g/dl	1701	9.9 (8.8-11.2)	458	9.3 (8.5-10.6)	0.001
Haematocrit (%)	918	25.9 (22-31.9)	245	24.6 (21.8-30)	0.016
Serum Ferritin (ng/mL)	143	83 (42-246)	45	64 (42-141)	0.446
Serum Cholesterol (mg/dl)	433	154 (126-184)	122	142 (120-174)	0.062
Serum Phosphorus (mg/dl)	861	5.5 (4.3-6.8)	234	5.4 (4.2-6.7)	0.568
Serum Calcium (mg/dl)	968	9 (8-9.8)	272	8.8 (7.9-9.6)	0.158
Predialysis creatinine (mg/dl)	982	10.2 (8-12.4)	258	9.4 (7.3-11.7)	0.008
Predialysis urea (mg/dl)	1000	120 (85-154)	296	142 (86-170)	0.001

*Number of patients with valid data for each variable
Values are median (interquartile range) or mean± standard deviation

Table 8. 2: Baseline data grouped according to survival status at 1 year. (Categorical variables)

	Outcome of dialysis patients				
	Survived N=1701		Died N=458		P-value
	Number*	Value (%)	Number*	Value (%)	
Male	1701	962(56.6)	458	271 (59.2)	0.171
Married	1174	793 (67.5)	341	289 (84.8)	0.001
White	1664	1465 (88)	446	379 (85)	0.091
Higher education	1048	430(41)	300	90 (30)	0.001
Physically dependent	1197	303 (25.3)	343	147 (42.9)	0.001
Current smoker	1183	156 (13.2)	332	31 (9.3)	0.034
Diabetic	1701	437 (25.7)	458	223 (48.7)	0.001
Previous cerebrovascular accidents	1241	88 (7.1)	360	71 (19.7)	0.001
Haemodialysis	1701	1685 (99.1)	458	448 (97.8)	0.033
Planned onset of dialysis	1204	79 (6.6)	347	40 (11.5)	0.002

*Number of patients with valid data for each variable

Binary logistic regression analysis was used to identify independent risk factors for increased 1-year mortality. Cases with missing variables were excluded, thus 1189 cases were included in this analysis. Independent variables used in the analysis were: age at onset (years), physically dependent, diabetes, HD hours per week and predialysis urea. Results are shown in Table 8. 3.

Table 8. 3: Independent risk factors for increased 1-year mortality in dialysis patients

	HR	95.0% CI	P- value
Age at onset (years)	1.037	1.027-1.047	<0.0001
Physically dependent	1.818	1.333-2.480	<0.0001
Diabetes	1.479	1.078-2.028	0.015
Predialysis urea	1.004	1.001-1.007	0.002

Hosmer and Lemeshow test for goodness of fit P- value =0.995; Nagelkerke R Squared=0.164

8. 4. Discussion

This study is the first comprehensive assessment of survival in patients receiving dialysis in Libya. The crude annual mortality rate of 21.2% is similar to that reported in many other countries. A death rate of 26.4% was reported in the Saudi dialysis population (309) while in Jordan the rate was 20% (20). Afifi and Karim reported annual mortality of 11.7% in Egypt (286). In Syria, the three-year survival rate ranged from between 26% to 64% in different dialysis centres (310). A previous study in a single dialysis unit in Libya showed an overall 5-year mortality rate of 51.4% (311) which was higher than the United States and the UK (312). The annual mortality rate in dialysis patients has declined in the United States but it is still high for certain groups, exceeding 20%. In Europe, it has been reported to be 19.8% (313) while in the UK it ranged from 14.6% to 18.4% in different regions (314). In Japan the annual death

rate has improved progressively (315, 316) and recently it has been less than 10% (174). Qatar has also reported a reduction in the annual mortality rate from 11% in 2002 to 7% in 2006 (16).

Despite the apparently favourable comparison with survival on dialysis in other countries, it should be noted that the median age of dialysis patients, an important determinant of survival, is substantially lower in Libya than in most developed nations. Thus survival on dialysis is low compared with many other countries. The reasons for this relatively poor survival require further investigation but it is likely that multiple factors are involved. Our observation that patient who died had lower median hours per week of dialysis and higher predialysis urea suggests that delivered dialysis dose may be one factor. The lower serum albumin and haemoglobin observed in those who died may reflect poorer nutrition and inadequate management of anaemia but both albumin and haemoglobin are negative acute phase reactants and may therefore be a marker of other disease processes that account for increased mortality. Higher predialysis systolic blood pressure in those who died may have contributed to deaths due to cardiovascular disease. Pre-existing medical conditions also increase the risk of mortality on dialysis. Physical dependency, diabetes and previous cerebrovascular events were more common in those who died and the former two factors were independent determinants of survival. Nevertheless, the prevalence of comorbid conditions was relatively low, apart from diabetes. Thus an excess of comorbid conditions is unlikely to explain the observed high mortality rate.

The distribution of causes of death observed in our study was similar to that reported from most other countries (174, 314, 317). In common with almost all previous studies, cardiovascular and cerebrovascular disease accounted for the majority of deaths and infection was the second most common cause. On the other hand, our results revealed other causes of death which are not common in other countries such as anaemia/ bleeding, malignant hypertension, uraemia and liver failure. Death due to anaemia or bleeding suggests a lack of adequate blood transfusion services as well as inadequate resources for the treatment of anaemia whereas death due to uraemia implies that some patients are severely under-dialysed. It is very likely that some of the deaths due to uraemia result from inadequate dialysis due to a lack of sufficient dialysis capacity in some areas. The observation that sever hypertension is the cause of death in a small number of patients implies that attention to optimising fluid volume

status and treatment of hypertension is inadequate in some centres. Finally, the deaths due to liver failure are likely to have resulted from the very high prevalence of hepatitis C virus infection (31%) observed in dialysis patients in Libya.

Our results show a very wide variation in annual mortality in different units in Libya. The crude mortality rate in 7 units was higher than 30%. It is unlikely that this variation could be attributed wholly to variation in patient demographics or comorbidity profile and it therefore probably reflects variation in practices related to dialysis delivery. The observed variation suggests opportunities for improving outcomes by identifying best practice and standardisation of practice across all centres. At present there are no nationally accepted guidelines for dialysis in Libya and no renal registry to monitor outcomes. Moreover, many dialysis centres lack resources to monitor biochemical indicators and adequate monitoring of dialysis adequacy is achieved in only a minority of patients (241). The development of clinical guidelines for dialysis in Libya or the adoption of international guidelines should be an urgent priority to improve survival and the establishment of a renal registry should be an important medium-term goal. Improved monitoring and treatment of high risk patients may also help to improve survival and our results indicate that efforts should focus on high-risk groups including the elderly, those who are physically dependent and those with diabetes.

Our study has several limitations. A small proportion of patients were lost to follow-up and it is likely that some of these died, implying that our observed annual mortality rate may be slightly lower than the true mortality rate. Medical records were unfortunately incomplete in many cases and we therefore had to rely on patient histories for information regarding past medical history (although the ability to independently corroborate historical data by direct patient interaction may be seen as a strength). Thirdly, the causes of death could not be accurately confirmed as many deaths occurred outside the centre and/or the local hospital. Finally, the short follow-up period enabled us to prospectively determine the crude 1-year mortality rate but a longer study period would provide a more comprehensive description of survival trends.

8. 5. Conclusion

Patients receiving dialysis in Libya have a crude 1-year mortality rate similar to most developed countries but the mean age of the dialysis population is much lower and this

outcome is thus relatively poor. As in most countries, cardiovascular disease and infection were the most common causes of death. Variation in mortality rates between different centres suggests that survival could be improved by promoting standardisation of best practise.

Chapter 9

Discussion, conclusion, limitations, implication and future work

9. Discussion, conclusion, limitations, implication and future work

9.1. Discussion

We aimed to undertake a comprehensive description to the epidemiology of dialysis-treated ESKD in Libya and assess the provision of dialysis services in the country. Libya is a low populated medium developed country and is the 4th largest country in Africa. Most people live in the North of the country but there are many small communities scattered throughout the country which represent a challenge to health care authorities to deliver high quality services to minorities in remote places especially in the Sahara. Large distances between cities create difficulties in terms of providing necessary staff and regular supplies as well as maintenance services (318-320).

Initially, we assessed the feasibility of using information from the Ministry of Health and the national drug and medical supplies company. Therefore, we contacted them to obtain an updated list of the functioning maintenance dialysis facilities in the country as well as the number of patients receiving treatment in each facility. We were surprised to discover that this information was not held by the Ministry. Moreover, there was no renal registry or any alternative body monitoring the delivery of dialysis treatment. We found that there were no clear means of communication between the Ministry of Health and dialysis centres or between dialysis centres themselves. There were no contact details available for most dialysis facilities. Therefore, we created the first comprehensive list of dialysis facilities and their contact details by contacting each hospital in the country to enquire about provision of dialysis services either within the hospital or as a satellite unit supervised by the hospital. In addition, we tracked the delivery of dialysis consumables from the main stores to the distribution points. Finally, we identified 40 functioning maintenance dialysis facilities by May 2009 (one of them serving children only). We established communications with the clinical managers in each facility and contacted them by mobile telephone. This initial phase of the study therefore identified a major

weakness in the provision of dialysis in Libya, namely a lack of central co-ordination of services and monitoring of quality or outcomes. It is vital that this shortcoming is overcome if the quality of dialysis provision is to be improved. Establishing the first comprehensive list of facilities and their contact details through this study will hopefully be the first step in this improvement.

After initial assessment through field visits to 5 dialysis facilities, we realised that we would have to collect the required data in person rather than depending on local dialysis staff to provide us with information about each dialysis patient. This decision was taken to ensure the validity and consistency of information and also because we found that dialysis staff in the large capacity facilities were very busy and could not find time to collect and document the required information. Another important consideration was the observed low quality of medical records, which were often incomplete; necessitating the use of alternative sources such as patient interviews, biochemical results folders and staff interviews (we observed that many dialysis nurses have good knowledge of their chronic dialysis patients). Therefore we set a time table and arranged visits with the clinical managers of 28 facilities. We travelled throughout the country and visited all medium and large size maintenance dialysis facilities (n=28) where we interviewed the clinical managers as well as all patients. We relied on telephone phone interview for the remaining small facilities to collect the required information about the dialysis provision and sent data collection forms to be completed by the staff in these facilities.

Our results showed that maintenance dialysis was provided in all regions of Libya. Services were freely accessible for all nationals as well as residents. Non- residents were charged for treatment. Maintenance dialysis was provided only by the public sector. All supplies and consumables were imported from overseas through a single provider (Ministry of Health) who contracted with different producers. The supplies and consumables were unloaded in a central store in Tripoli then distributed to 3 main regional stores for distribution. All facilities provided HD but only three provided CAPD to a minority of patients. Large capacity, purpose built facilities were located in the 2 main cities, Tripoli and Benghazi. However, most dialysis facilities in the country were in buildings originally built for a different purpose. To respond to increasing demand on dialysis, almost all dialysis facilities has undergone expansion by fitting

in more HD stations at the expense of space. Work load varied widely where some dialysis facilities were working to maximum capacity while others run only a few sessions per week. This practice reflects lack of integration in health care planning. There were a considerable number of HD machines in the facilities but many of them were non-functioning. Weak technical support particularly in remote areas resulted in an accumulation of non functioning HD machines in each facility which is a waste of health care resources. For example, 28% of HD machines in the Southern region of the country were non-functioning. All dialysis facilities reported intermittent shortage of most types of medication, supplies and reagents needed for laboratory testing. Managers solve these problems by a variety of approaches including borrowing supplies from other dialysis facilities, temporarily reducing the frequency of dialysis, asking patients to buy the needed medication or laboratory testing on their own expenses from the private sector. Interrupted supplies reduce the quality the services and reflect suboptimal organisation of the health care system.

We also observed that the number of expert nephrologists was extremely low and most patients were managed by internists and untrained medical graduates. The deficiency of expert nephrologists in the country reflects defective planning of graduate educational training. We observed that the ongoing patient management was mostly delivered by nurses. In the Southern region, there were two centres completely run by nurses.

Furthermore, our study showed that there are no national dialysis practice guidelines in use. Only a few practitioners were familiar with the NKF/KDOQI guidelines and they reported that they could not apply most of them due to local constricts such as interruption of supplies and medication. Lack of clinical practice guidelines, deficient training and lack of auditing in Libya have resulted in variable approaches to dialysis patient management. We observed that the majority of practitioners in dialysis centres relied on clinical monitoring and monthly pre-dialysis urea concentration measurements which are an unreliable measure of dialysis adequacy. The use of the most widely accepted measure of dialysis adequacy Kt/v was limited to small numbers of patients, despite capacity for online measurement of Kt/v being available in most HD machine types used in Libya. The approach to biochemical assessment also varied widely where a number of facilities were not monitoring serum ferritin and total iron binding capacity, serum calcium and phosphorus, serum albumin and parathyroid hormone either due

to lack of facilities and/or lack of knowledge. We also observed a severe shortage of dieticians and social workers as well as educational materials in most facilities.

Other findings were that there were no water quality analysis reports in any dialysis facilities. In quarter of dialysis facilities, water samples for biological quality were collected during the year prior to the study but results were never reported. Furthermore, we found that the large amount of waste generated from daily dialysis activities was mostly treated by dumping or open air incineration alongside the domestic waste, creating a significant environmental hazard. (figure 9.1)

Figure 9. 1: waste generated from daily dialysis activities collected in the backyard of a dialysis centre (Tripoli)

In the epidemiological study, we collected baseline information on all adults who were receiving maintenance dialysis in Libya. We could not access information about the cases of ESKD who were transplanted or died before being referred to maintenance dialysis facilities because of the lack of a registry for such cases. Therefore, the incidence of ESKD we observed probably underestimates the true incidence of ESKD. We interviewed all patients who gave

consent, n=1766 patients (73.1% of all adult dialysis- treated patients in Libya) from 28 dialysis facilities and we collected additional information from their medical records and treating staff. We applied a structured questionnaire which enabled us to gather a wide range of epidemiological and medical information as well as information about specific aspects in dialysis including HBV and/or HCV infection and vascular access. We gathered data from the small facilities by sending data collection forms for completion by staff and added them to the information collected through field visits. We ultimately managed to determine the prevalence and causes of ESKD in adult patients receiving maintenance dialysis in Libya in August 2009. At the same time, we established a prospective collection of information about all new patients who started dialysis from September 2009 to August 2010 in order to determine the incidence of dialysis-treated ESKD in Libya.

Our results showed a remarkably higher prevalence of ESKD (624 pmp) than the rates observed in other countries in the Middle East region despite racial, socioeconomic and environmental similarities. Most prevalent patients were of economically active age with peak prevalence rate at 55-64 years. The diagnosis of primary kidney disease was clinical in most cases. Reasons for reliance on clinical rather than histological diagnoses include lack of guidelines, limited resources and pathology services and late presentation of patients with ESKD. Accurate diagnoses supported by histopathology reports were found in only a few patients. Diabetes was the most important cause of ESKD affecting 41.1% of those who were 50 years or more. The high prevalence of diabetes in the general population could be an important reason for high prevalence of ESKD observed in Libya, although the prevalence of diabetes is even higher in other Middle Eastern countries. Weak PHC and poor management of diabetes may contribute to the high risk for acquiring ESKD. Another interesting observation was the high proportion of ESKD caused by congenital and hereditary diseases in addition to polycystic kidney disease. The burden of these diseases could be reduced by genetic counselling and early management. However, weak preventive services in Libya and limited access to genetic counselling likely contribute to the observed high prevalence rate.

We found a high incidence rate for ESKD (282 pmp) during our 1-year follow up study. The number of new patients starting dialysis in one year was 45% of the prevalent number at baseline. This rate is among the highest in the world, only slightly lower than in Japan (287

pmp) despite a substantially lower median age for the general population in Libya. Moreover, our incidence rate was approximately double the rate reported from neighbouring Tunisia despite cultural and economic similarities between the countries. Our results also showed substantial differences between regions, with the highest incidence rate of 617 pmp observed in the South of Libya. The Southern region is the lowest populated area in the country and is the most socially and economically deprived region. It is also inhibited by a mix of people originating from different tribes. Racial disparities and social deprivation have been described as a risk factor for ESKD due to poverty, malnutrition, low educational levels, exposure to heavy metals and limited access to healthcare (321, 322).

While assessing the provision of dialysis services in Libya, we observed that staff were applying variable practices to control nosocomial transmission of infection. Again, there were no guidelines to direct infection control measures. Nevertheless, sero-positive patients were dialysed on dedicated machines either in an isolation area or alongside sero-negative patients if space did not allow isolation. There were no previous reports about the prevalence, incidence and risk factors of HBV and/or HCV infections in the HD population of Libya. Therefore, in this part of the study, we focused on these infections. We included all adult patients receiving maintenance HD during May 2009 in all centres over the country (n=2382) and excluded CAPD-treated patients. We found that the overall prevalence of HBV and/or HCV infections in HD population was 34.9%. However, the prevalence of HBV infection was similar to the general population of Libya despite our previous observation that HBV vaccination was administered in only 26% of dialysis centres. On the other hand, the prevalence of anti-HCV antibodies observed in patients receiving HD (31.1%) was remarkably high and is approximately 25 times higher than in the general population. Additionally, we observed that sero-positive patients had a longer time on dialysis and more previous blood transfusions which were highly suggestive of nosocomial transmission. Moreover, we observed that the prevalence of HBV±HCV infection varied widely between HD centres from 0% to 75.9%, implying that variable infection control measures contributes to variable rates of nosocomial infection.

To determine the incidence of new HBV and/or HCV infections during 1 year, we followed up all previously interviewed sero-negative HD patients. Our results revealed an incidence of

sero-conversion of 7.7% during 1 year (7.1% HCV; 0.6% HBV). The rate of new HCV infections was more than rates reported in dialysis patients in many other countries. Wide variation in rates of newly acquired infections was observed between dialysis centres. All new HBV cases were referred from centres already treating HBV infected patients, suggesting cross infection between patients in the same dialysis centre. New HCV infections were reported in most centres but the rate of HCV sero-conversion varied widely from 1.5% to 31%. This result might reflect variation in nosocomial control polices between centres as well as anaemia management and quality of blood screening procedures. Risk factors significantly associated with sero-conversion included; duration of dialysis, history of previous renal transplant and history of receiving HD in another centre in Libya.

We explored the patterns of vascular access in patients receiving maintenance HD in Libya by analysing information about 1712 HD patients who were interviewed in 25 HD facilities. Our results showed that the majority of HD patients were using permanent vascular access in the form of AVF. AVG use was very limited to only 4.4% of total number of patients included in this part of the study. High achievement of AVF use was found despite our previous observation that only 15% of dialysis facilities in Libya were providing permanent vascular access services. Nevertheless, our results showed that most HD patients had commenced their treatment via a temporary CVC which reflects poor predialysis preparation and inability of the health care system to detect cases of CKD early and refer them for management in a specialist service when appropriate. The problem is further exacerbated by limited access to vascular surgery resulting from shortage of trained surgeons in this field as well as a shortage of radiological equipment needed for assessment and vascular mapping. Our results show that permanent vascular access was more likely to be placed in the forearm in males as compared to females. Results also showed that the thrombosis rate of both forearm and upper arm fistula was less in males as compared to females.

We further assessed outcomes related to vascular access in 1-year follow up study. All patients who were using permanent vascular access for dialysis at the time of the first interview were included. Results showed that the incidence of permanent VA thrombosis was 14.7% and was significantly more common among female patients. Hospitalisation for vascular access related complications was reported by 31.4% during the 1-year period.

The final step in our study was to determine the outcome of all patients who were receiving maintenance dialysis during May 2009 after monitoring them for 1-year period. Our results showed that the annual crude mortality rate (21.2%) was within the range reported in many developed countries but the mean age of the dialysis population in Libya was approximately 2 decades lower than these countries and the survival rate is therefore relatively poor. Patient characteristics that were identified by binary logistic regression analysis as independent determinants of increased mortality included; age at onset of dialysis, physical dependency, diabetes and elevated predialysis urea.

The unsatisfactory survival rate on dialysis could be explained by multiple factors including lack of training, auditing and communication between centres, shortage of qualified nephrologists and deficient monitoring of the biochemical indicators. We observed that dialysis practices in Libya were outdated in most facilities and inherited unsatisfactory practices were common. The suboptimal monitoring of dialysis patients was reflected by high median blood pressure values, low time on HD per week, low haemoglobin and haematocrit concentrations and low serum albumin concentration. Our results showed that there was large variation in mortality rates between different centres with annual mortality rates reaching 70% in a few centres.

9.2. Conclusion

ESKD in Libya is a major health problem where the incidence rate is among the highest in the world. Despite rapid expansion of dialysis services throughout the country, our study has identified that many aspects of dialysis provision are suboptimal and that outcomes are relatively poor. We have identified several major challenges to improving the quality of dialysis provision including lack of dialysis practice guidelines, absence of auditing and quality control and limited access to kidney transplantation. As Libya reorganises its health services in the post-conflict period it is hoped that this study will be the first step in establishing a renal registry and that the areas of concern highlighted will prompt the implementation of national clinical practice guidelines for dialysis.

9. 3. Limitations

While this study has provided the first nationwide description of the epidemiology and treatment of dialysis- treated ESKD in adult population of Libya, there were a number of limitations that should be conceded. Researchers faced difficulties in collecting data because the medical records maintained by most dialysis facilities included only details of dialysis treatments. Information related to past medical history, diagnosis of primary kidney disease, co-morbidities, complications and hospitalisations as well as biochemical investigations was generally held in hospital inpatient records. Thus researchers frequently were forced to use other sources such as patients and staff interviews as well as collecting information from hospital archives. When assessing vascular access-related complications we mostly relied on information obtained from patients and staff rather than medical or laboratory reports. Cause of death was also often obtained from the staff when not documented in the medical records.

We could not obtain detailed data for the 35 patients who were receiving CAPD in Libya because of deficient medical records which could not be overcome by interviewing patients as these patients attend the dialysis facilities only once monthly.

Because of time, resource and transport constrains we could not visit 12 small capacity dialysis facilities. We collected information through pre-prepared data collection forms and frequent phone calls. Most of these facilities are in remote and deprived areas and are among the dialysis facilities with poorest outcomes. Despite observing clear ethnic variation in the incidence and prevalence of ESKD, we could not determine exact rates in minority populations in Libya as the information about ethnic distribution of the general population is not documented in the national statistics. Reporting HBV and/or HCV infections and seroconversion was based on serological testing which was done in local laboratories and it is likely that there was some variation in the quality of testing. Testing for HCV relied on a third generation ELISA to detect anti-HCV antibodies and was recorded in each patient's medical record but confirmation or genotyping with PCR was not available.

9. 4. Implications

This study has several important implications for health care policy-makers and managers of dialysis facilities. Despite adequate funding for dialysis services and rapid expansion to meet the population's needs, we have identified numerous severe deficiencies in the current system:

- The healthcare service currently does not have adequate systems in place to detect and treat CKD in its early stages. Investing in primary preventive services to reduce the incidence of ESKD is cost-effective because of the high cost of dialysis and transplantation. Common approaches include community based health education programmes and equipping PHC services to identify patients with CKD and treat them at an early stage. Clear referral guidelines will promote timely referral for dialysis preparation and reduce the number of unplanned dialysis initiations.
- We have observed wide variations in practice as well as outcomes between dialysis facilities. The development and implementation of dialysis practice guidelines will standardise best practice and improve the quality of dialysis provision.
- The establishment of a national renal registry and standardisation of medical records should be regarded as an urgent priority. Analysis of data returns acts as a valuable feedback tool for patients, staff and providers in dialysis facilities. Moreover, it yields longitudinal descriptions of ESKD trends as well as treatment and assists national and international comparisons.

9. 5. Future work

Our findings have highlighted the need for more studies in this field because it generated several unanswered questions, including;

- ESKD usually represents the "tip of the iceberg" of CKD in a community. Therefore, population-based studies are required to describe the extent of CKD in Libya to plan preventive and therapeutic services for affected people.

- The contribution of congenital and hereditary diseases to incidence and prevalence of ESKD reported in this study is relatively high. An investigation of modes of inheritance and the role of consanguity might help in planning counselling services.
- We have reported a very high prevalence and incidence of HCV infection in dialysis facilities. This should prompt an urgent detailed assessment of infection control procedures and implementation of best practice in all centres.
- Further studies are needed to investigate practices relating to the disposal of dialysis-related medical waste to improve safe practice and reduce the impact on the environment.
- Our finding that no chemical or biological monitoring of dialysis water quality was reported to dialysis facilities warrants prompt investigation.
- Providing maintenance dialysis is a multidisciplinary task. We reported suboptimal staffing including; shortage of trained nephrologists, social workers, dieticians and vascular access surgeons and coordinators. More studies are needed to explore the obstacles to providing necessary staffing.
- Fortunately, our second round of data collection ended one month before the revolution and associated war in Libya. The impact of the conflict on dialysis provision and outcomes should now be investigated.

Chapter 10

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10. References

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Annex

Dialysis Centre Questionnaire

□ Visit □ Phone

Date..... Location of dialysis centre □Inside a hospital □ Free standing

Centre name ..... City ..... Tel .....

Centre start date ..... Type of dialysis provided.....

Number of dialysis rooms ..... Number of all stations .....

Number of working stations ..... Working days/week .....

Total number of patients ..... Number of CAPD patients .....

Minimal age of patients ..... Maximum age of patients.....

Presence of nephrology clinic □Yes, in unit □Yes, in hospital □No

Frequency of patient monitoring by a nephrologists HD..... PD.....

Dialysis adequacy monitoring □No □Yes Type ..... Frequency .....

Application of dialysis practice guidelines □Yes □No If yes, type

.....

Time on HD for registered patients ..... Frequency/week .....

Number of junior nephrologists ..... Number of senior nephrologists ..... Number of nurses .....

Staffing

Working shifts	Number of patients	Number of junior nephrologists		Number of senior nephrologists		Number of dialysis nurses	Number of social workers	Number of technicians
		Present	On call	Present	On call			
Morning								
Afternoon								
Evening								

Isolation of infected cases □Yes □Some □No

Type of isolation □ Group □Individual

Isolation for septic patients □Yes □Some □No

Hand wash facility in each room □Yes □Some □No

Hand disinfection □Yes □Some □No

Use of gloves □Yes □Some □No

Machine disinfection □Yes □No

Method of waste disposal .....

Sharps separation .....

Dialyser reuse □Yes □No

Availability of dietician □No □In unit □In hospital

Number of patients waiting for HD .....

Availability of pharmacy □Yes □No

Availability of Medicines □Yes □Some □No

Availability of Eperax □Yes □Some □ No

Availability of IV Iron □Yes □Some □ No

Patient education □Yes □Some □ No

Provision of vascular access surgery □Yes, in unit □Yes, In hospital □No

Water source .....

Water treatment □Yes □No

Water quality test □Yes □No

Biological □Yes □No Chemical □Yes □No Frequency .....

Frequency of viral screen testing .....

Availability of laboratory investigations in the centre

Availability of laboratory investigations	Frequency	Availability of laboratory investigations	Frequency	Availability of laboratory investigations	Frequency
Haemoglobin		Triglycerides		Phosphorus	
Haematocrit		Cholesterol		Total proteins	
Serum Ferritin		LDL		PTH	
Fasting blood sugar		Liver Function Tests		Kt/v	
HbA1c		Electrolytes		Serum Albumin	
TIBC		Uric Acid		Predialysis urea	
Serum Iron		Calcium		Post dialysis urea	

Dialysis Patient Questionnaire

ID ..... Date ..... Centre .....

File number..... D.O.B..... Sex..... Nationality.....

Ethnicity □White □Black Marital status..... Number of children.....

Level of education..... Occupation..... Working at present □Yes □No

Independent □Yes □Partially □No Cause of dependency

.....

H/O smoking □Yes □No Years of smoking ..... Smoker now □Yes □No

Presence of pre dialysis health problems..... Types of pre dialysis health problems.....

Duration in years.....

Mode of treatment..... Weight..... Height.....

Onset of ESRD □Sudden □Gradual □Planned (fistula prepared)

Presenting symptoms .....

H/O admission at onset..... Duration .....

Cause of ESKD .....

Family H/O ESKD □Yes □No

Number of relatives ..... Relationships .....

Renal biopsy taken □Yes □No Histopathology result .....

Date of 1st dialysis ..... Change in modality □Yes □No

Nephrology follow up □Yes □No □Irregular □Regular at .....

Rounds at dialysis centre □Routine □On demand □No

Frequency of laboratory investigation .....

H/O vaccination □Yes □No Types of vaccine used.....

Blood transfusion □Yes □No Frequency .....

Vascular access site .....

Type of vascular access □ Native fistula □Graft □Permanent catheter □Temporary C

□CVC H/O vascular access block □Yes □No

Frequency .....

H/O vascular access complications □Infection □Aneurysm □Bleeding

H/O HD abroad..... Name of country.....

H/O HD in other centre in Libya .....

HD sessions per week ..... HD/hrs per each session .....

H/O renal transplant □Yes □No

Pre dialysis BP ...../ ...../ .....

Post dialysis BP ...../ ...../ .....

Viral infection □Yes □No Time diagnosed □Predialysis □Post dialysis

Type of virus □HIV □HBV □HCV

H/O hospitalisation after HD: Number .....

Duration.....

Causes .....

H/O hospitalisation during the previous year: Number .....

Duration.....

Causes .....

Medication taken by the patient at present

Eprax □Yes □No

IV Iron □Yes □No

Other.....

Results of available recent laboratory test

Test	Value	Test	Value	Test	Value
Haemoglobin		Haematocrit		Triglycerides	
Serum Albumin		Total lipids		Total proteins	
HbA1c		Cholesterol		PTH	
Serum Iron		LDL		Uric Acid	
Serum Ferritin		Alanine aminotransferase		Creatinine	
TIBC		Aspartate aminotransferase		Predialysis urea	
Fasting blood sugar		Alkaline Phosphatise		Post dialysis urea	
Phosphorus		Calcium		Other	