INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem. The prevalence of end-stage renal disease (ESRD) is increasing ***(Szczech et al., 2004)***. Although the exact reasons for the growth of the ESRD program are unknown, changes in the demographics of the population, differences in disease burden among racial groups and under-recognition of earlier stages of CKD and of risk factors for CKD, may partially explain this growth ***(McClellan et al., 1997).***

There is a large body of evidence that patients with ESRD have a substantial increase in cardiovascular and Non-Cardiovascular complications. Cardiovascular complications are the main cause of morbidity and mortality in dialysis patients which are known to be enhanced by accelerated atherosclerosis occurring in those patients that add to the preexisting hypertension, ischemic heart disease, peripheral vascular disease and/or cerebro-vascular disease ***(Benedetto et al., 2005)***. Impact of volume overload which can occur second to decrease urine output and also the impact of hyper-dynamic circulation that caused by Arterio-venous fistula can add to cardiac overload and worsen the ischemic cardiomyopathy present ***(Sarnak et al., 2000)***.

The non-cardiovascular complications with direct impact on morbidity and mortality are mainly like Anemia that can cause decrease tissue oxygenation and more worsen the

existing ischemic changes of heart, brain and other tissues ***(Nurko, 2006)***. The mineral disturbance in those patients will lead to the famous bone diseases like Osteitis fibrosa cystica, also lead to hyperparathyroidism with consequent calcifications in soft tissues ***(Dusilová Sulková, 2011)***. With Anemia and Mineral disturbance also compliance of HD and recurrent infections, malnutrition and dyslipidemia have direct impact on morbidity and mortality ***(Bammens et al., 2003, Chmielewski et al., 2008)***.

Some other complications with less significant effects can occur like psychiatric disorders ***(Kimmel et al., 1998),*** Sexual dysfunction ***(Miyata et al., 2004),*** Peripheral neuropathy, dialysis related amyloidosis, some bleeding disorders secondary to platelet dysfunction and Cutaneous manifestations ***(Dember et al., 2006)***. Access complications like failure, thrombosis and infections are out of scope of this study.

AIM OF THE WORK

To search for and focus on the prevalence of the complications in patients on chronic hemodialysis (HD) taking in consideration the impact of duration of CKD and HD and the compliance to HD.

Chapter One

HEMODIALYSIS

Definition

Dialysis is defined as the diffusion of molecules in solution across a semipermeable membrane along an electrochemical concentration gradient ***(Depner, 1991)***.

Goals of Hemodialysis

The primary goal of hemodialysis is to restore the intracellular and extracellular fluid environment that is characteristic of normal kidney function. This is accomplished by the transport of solutes such as urea from the blood into the dialysate and by the transport of solutes such as bicarbonate from the dialysate into the blood (Fig. 1A). Solute concentration and molecular weight are the primary determinants of diffusion rates. Small molecules, such as urea, diffuse quickly, whereas compartmentalized and larger molecules, such as phosphate, β2-microglobulin, and albumin, and protein bound solutes, such as p-cresol, diffuse much more slowly (Fig. 1B and 1C). In addition to diffusion, solutes may pass through pores in the membrane by means of a convective process driven by hydrostatic or osmotic pressure gradients; a process called ultrafiltration ***(Locatelli et al., 2002)***. During ultrafiltration, there is no change in solute concentrations; its

primary purpose is the removal of excess total body water ***(Himmelfarb and Ikizler, 2010)***.

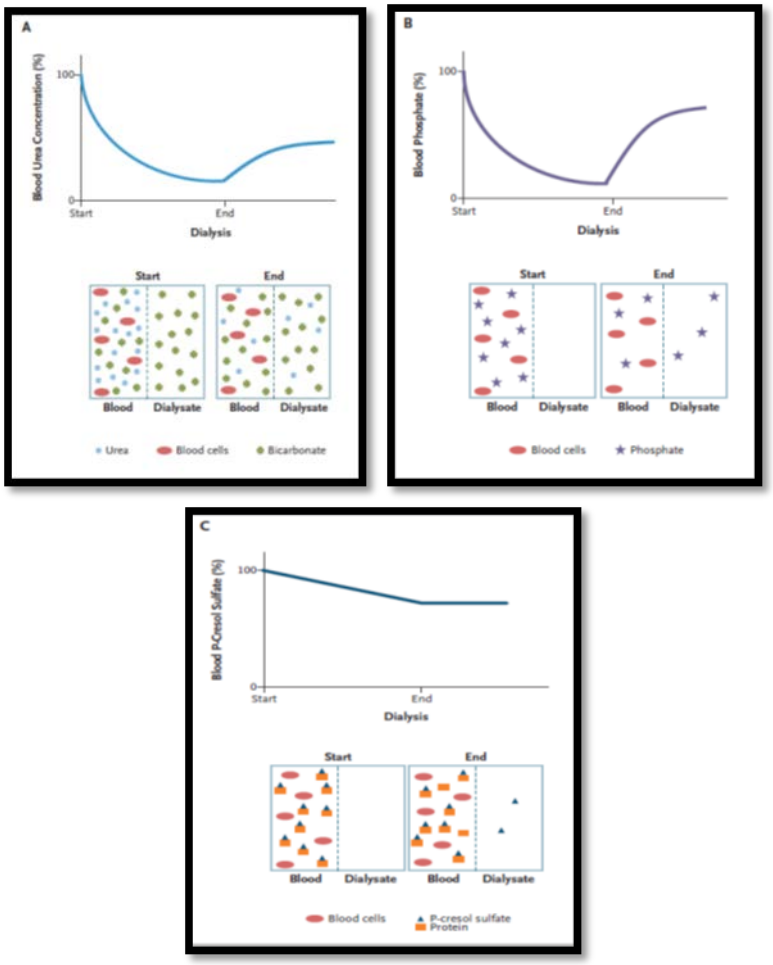

Figure 1: Patterns of Solute Removal with Hemodialysis. Low-molecular-weight solutes such as urea are readily dialyzed (Panel A). For compartmentalized solutes, such as phosphate, the plasma space is rapidly cleared (Panel B), whereas most phosphate in cells and bone remains there. Dialysis of protein-bound solutes, such as p-cresol sulfate, is limited because protein binding limits the free-solute concentration, which is the driving force for diffusion (Panel C) ***(Himmelfarb and Ikizler, 2010).***

For each dialysis session, the patient's physiological status should be assessed so that the dialysis prescription can be aligned with the goals for the session. This is accomplished by integrating the separate but related components of the dialysis prescription to achieve the desired rates and total amount of solute and fluid removal (Table 1). By replacing kidney excretory function, dialysis is intended to eliminate the symptom complex known as the uremic syndrome, although ascribing particular cellular or organ dysfunction to the accumulation of specific solutes in uremia has proved to be difficult ***(Meyer and Hostetter, 2007)***.

Table 1: Key Components of the Hemodialysis Prescription *(Himmelfarb and Ikizler, 2010)*

Component	Comments
Dialyzer	
Configuration	Hollow-fiber dialyzers are preferred owing to improved safety.
Membrane biomaterials	Synthetic membranes are used more frequently than cellulose membranes owing to fewer blood–membrane interactions.
Membrane permeability	High-flux membranes are constructed with larger pores, which allow greater removal of higher-molecular-weight solutes, with similar removal of lower-molecular-weight solutes as compared with low-flux membranes.
Treatment time	Usual treatment time is about 4 hours. Longer treatment times allow more fluid removal with less risk of intradialytic hypotension, and the removal of compartmentalized solutes such as phosphate is increased; nevertheless, increased dialysis time has limited effects on removal of many solutes because of decreasing plasma concentrations.
Treatment frequency	Usual frequency is 3 times per week. Increasing the frequency of dialysis to >3 times per week improves solute clearance and fluid removal; effects on clinical outcomes and quality of life are being evaluated in randomized trials.
Blood flow rate	Usual prescription is 200 to 400 ml per minute. Achievable blood flow depends on the type and quality of vascular access. Increasing blood flow increases solute removal; however, increased flow resistance will eventually limit the augmented clearance.
Dialysate flow rate	Usual rate is twice the achieved blood flow rate in order to attain near-maximal solute clearance.
Ultrafiltration rate	Should be less than 10 ml per kilogram of body weight per hour to reduce the risk of intradialytic hypotension.
Dialysate composition	
Sodium	Between 130 and 145 mmol per liter. Higher sodium concentrations decrease the risk of intradialytic hypotension but increase thirst and interdialytic weight gain.
Potassium	Generally 2 to 3 mmol per liter. Lower levels of dialysate potassium are associated with sudden cardiac death; intradialytic potassium removal is highly variable, and plasma potassium levels rebound about 30% after dialysis.
Calcium	Generally 1.25 to 1.75 mmol per liter. Only non–protein-bound calcium is removed; higher levels of dialysate calcium increase intradialytic blood pressure.
Magnesium	Generally 0.5 mmol per liter. The optimal level of magnesium is unresolved, and magnesium flux is difficult to predict.
Alkaline buffers	Commonly 30 to 40 mmol per liter. Predominantly bicarbonate with a small amount of acetate; bicarbonate concentration can be adjusted to correct metabolic acidosis.
Chloride	Defined by prescribed cations and alkaline buffers in dialysate.
Glucose	Commonly 100 to 200 mg per deciliter. Higher levels of glucose promote hypertriglyceridemia.
Intradialytic medications	Erythropoietin, iron, vitamin D analogues, antibiotics.
Anticoagulation	Heparin or other agents.

Initiation of dialysis

Optimum timing of treatment for patients with CKD prevents serious and uremic complications, including malnutrition, fluid overload, bleeding, serositis, depression, cognitive impairment, peripheral neuropathy, infertility, and increased susceptibility to infection. However, all forms of kidney replacement therapy entail important trade-offs. As GFR decreases, patients and physicians must weigh many risks and benefits. Decision making is more complex for older and more fragile patients. In some cases, social and psychological factors may lead to earlier dialysis therapy initiation, and in some cases, to later initiation ***(Levin and Rocco, 2006)***.

The initiation of dialysis therapy remains a decision informed by clinical art, as well as by science and the constraints of regulation and reimbursement. For some patients, conservative therapy, without dialysis or transplantation, is the appropriate option ***(Moss, 2001; Moss, 2003)***. If the patient makes this choice, the health care team should strive to maximize QOL and length of life by using dietary and pharmacological therapy to minimize uremic symptoms and maintain volume homeostasis. These include, but are not limited to, use of low-protein diets, ketoanalogs of essential amino acids, loop diuretics, and sodium polystyrene sulfonate (***Levin and Rocco, 2006)***.

Preparation for Kidney Failure

Timely Education in Stage 4 CKD

Timely patient education as CKD advances can both improve outcomes and reduce cost. Planning for dialysis therapy allows for the initiation of dialysis therapy at the appropriate time and with a permanent access in place at the start of dialysis therapy. Planning for kidney failure should begin when patients reach CKD stage 4 for several reasons. The rate of progression of kidney disease may not be predictable. There is substantial variability in the level of kidney function at which uremic symptoms or other indications for dialysis appear. Patients vary in their ability to assimilate and act on information about kidney failure. Local health care systems vary in the delays associated with patient education and scheduling of consultations, tests, and procedures ***(Levin and Rocco, 2006)***.

Timely education will: ***(Levin and Rocco, 2006)***

(1) Allow patients and families time to assimilate the information and weigh treatment options,

(2) Allow evaluation of recipients and donors for preemptive kidney transplantation,

(3) Allow staff time to train patients who choose home dialysis,

(4) Ensure that uremic cognitive impairment does not cloud the decision, and

(5) Maximize the probability of orderly and planned treatment initiation using the permanent access.

Contingency Plans:

Optimal timing of vascular access creation may depend on plans regarding transplantation and/or PD treatment.

Early attempts at native arteriovenous (AV) fistula creation are particularly important in patients who are:

(1) Not transplant candidates or

(2) Lack potential living kidney donors and also seem unlikely to perform PD. For patients hoping to undergo "preemptive" transplantation, thus avoiding dialysis treatment, the decision about whether to attempt AV fistula creation at CKD stage 4 (and, if so, when in stage 4) depends on the nephrologist's estimate of the likelihood that preemptive transplantation will be accomplished. For patients interested in performing PD, the decision about whether to attempt AV fistula creation at CKD stage 4 depends on the nephrologist's estimate of the probability that PD will be successful. The benefits of planning for kidney failure treatment are reflected in the literature comparing the consequences of early and late referral of

patients with CKD to nephrologists ***(Allon et al., 2001; Abdullah et al., 2005)***.

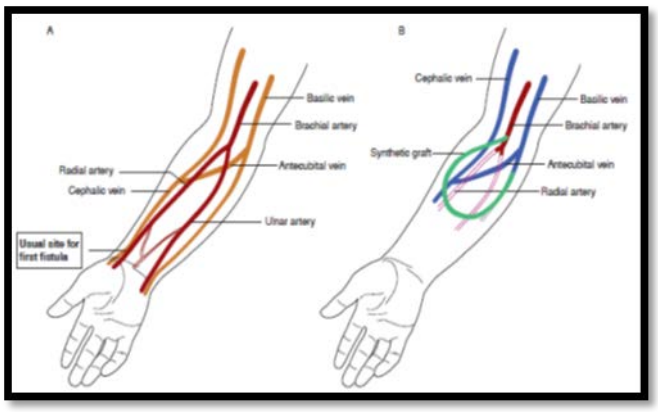

Figure 2: The predominant types of vascular access for chronic dialysis patients are *(A)* the arteriovenous fistula and *(B)* the synthetic arteriovenous forearm graft. The first primary arteriovenous fistula is usually created by the surgical anastomosis of the cephalic vein with the radial artery. The flow of blood from the higher-pressure arterial system results in hypertrophy of the vein. The most common AV graft (depicted in green) is between the brachial artery and the basilic or cephalic vein.

Education of Health Care Providers and Family Members:

Optimally, education in preparation for kidney failure will include not only the patient, but also other individuals who are likely to influence his or her decisions. These may include family, close friends, and primary care providers. Their understanding of such issues as the impact of interventions designed to slow progression, the absence of symptoms despite underlying kidney disease, transplantation eligibility, the choice between PD and HD, and the choice and timing of vascular

access may have critical consequences for the patient ***(Levin and Rocco, 2006)***.

Indications for Dialysis

As recommended by the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI), planning for dialysis should begin once the patient's glomerular filtration rate (GFR) or creatinine clearance (CLcr) drops below 30 mL/min per 1.73 m^2 ***(National Kidney Foundation, 2006).***

The primary criterion for initiation of dialysis is the patient's clinical status: the presence of persistent anorexia, nausea, and vomiting, especially if accompanied by weight loss, fatigue, declining serum albumin levels, uncontrolled hypertension or congestive heart failure, and neurologic deficits or pruritus. Some nephrologists use critical lab values of serum creatinine or blood urea nitrogen as indicators of when to initiate dialysis. The 2006 update of the K/DOQI guidelines suggest that benefits and risks of dialysis should be evaluated when estimated GFR or CL cr is <15 mL/min per 1.73 m^2 ***(National Kidney Foundation, 2006)***.

The advantages and disadvantages of hemodialysis and peritoneal dialysis are depicted in Tables 2 and 3, respectively. These factors, along with the patients' concomitant diseases, personal preferences, and support environments, are the

principal determinants of the dialysis mode they will receive ***(Foote and Manley, 2008)***.

Table 2: Advantages and Disadvantages of Hemodialysis

Advantages

1. Higher solute clearance allows intermittent treatment.
2. Parameters of adequacy of dialysis are better defined and therefore underdialysis can be detected early.
3. Technique failure rate is low.
4. Even though intermittent heparinization is required, hemostasis parameters are better corrected with hemodialysis than peritoneal dialysis.
5. In-center hemodialysis enables closer monitoring of the patient.

Disadvantages

1. Requires multiple visits each week to the hemodialysis center, which translates into loss of control by the patient.
2. Disequilibrium, dialysis hypotension, and muscle cramps are common. May require months before the patient adjusts to hemodialysis.
3. Infections in hemodialysis patients may be related to the choice of membranes, the complement-activating membranes being more deleterious.
4. Vascular access is frequently associated with infection and thrombosis.
5. Decline of residual renal function is more rapid compared to peritoneal dialysis.

Table 3: Advantages and Disadvantages of Peritoneal Dialysis

Advantages

1. More hemodynamic stability (blood pressure) due to slow ultrafiltration rate.
2. Increased clearance of larger solutes, which may explain good clinical status in spite of lower urea clearance.
3. Better preservation of residual renal function.
4. Convenient intraperitoneal route for administration of drugs such as antibiotics and insulin.
5. Suitable for elderly and very young patients who may not tolerate hemodialysis well.
6. Freedom from the "machine" gives the patient a sense of independence (for continuous ambulatory peritoneal dialysis).
7. Less blood loss and iron deficiency, resulting in easier management of anemia or reduced requirements for erythropoietin and parenteral iron.
8. No systemic heparinization required.
9. Subcutaneous versus intravenous erythropoietin or darbepoetin is usual, which may reduce overall doses and be more physiologic.

Disadvantages

1. Protein and amino acid losses through peritoneum and reduced appetite owing to continuous glucose load and sense of abdominal fullness predispose to malnutrition.
2. Risk of peritonitis.
3. Catheter malfunction, exit site, and tunnel infection.
4. Inadequate ultrafiltration and solute dialysis in patients with a large body size, unless large volumes and frequent exchanges are employed.
5. Patient burnout and high rate of technique failure.
6. Risk of obesity with excessive glucose absorption.
7. Mechanical problems such as hernias, dialysate leaks, hemorrhoids, or back pain more common than HD.
8. Extensive abdominal surgery may preclude peritoneal dialysis.
9. No convenient access for intravenous iron administration.

The HD system consists of an external vascular circuit through which the patient's blood is transferred in sterile polyethylene tubing to the dialysis filter or membrane (dialyzer) via a mechanical pump (Figure 3). The patient's blood then passes through the dialyzer on one side of the semipermeable membrane and is returned to the patient ***(Foote and Manley, 2008)***.

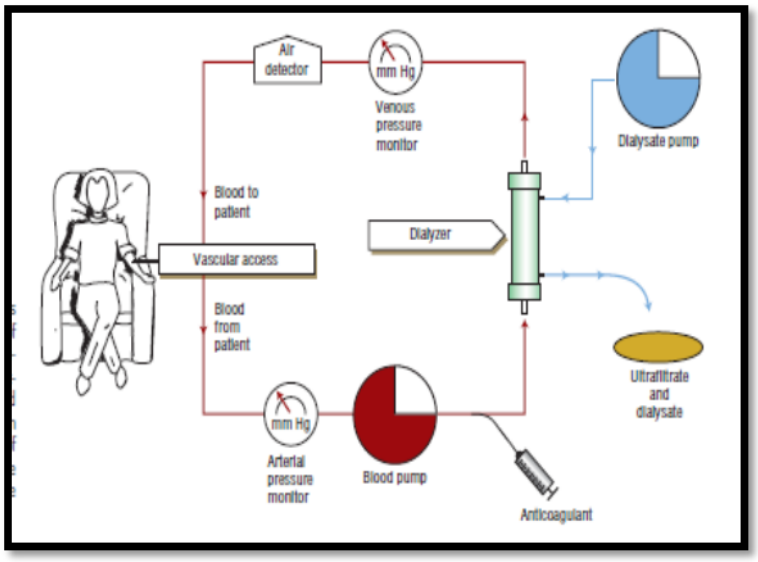

Figure 3: In hemodialysis, the patient's blood is pumped to the dialyzer at a rate of 300 to 600 mL/min. An anticoagulant (usually heparin) is administered to prevent clotting in the dialyzer. The dialysate is pumped at a rate of 500 to 1,000 mL/min through the dialyzer countercurrent to the flow of blood. The rate of fluid removal from the patient is controlled by adjusting the pressure in the dialysate compartment. ***(Foote and Manley, 2008)***

The dialysate solution, which consists of purified water and electrolytes, is pumped through the dialyzer countercurrent to the flow of blood on the other side of the semipermeable

membrane. In most cases, systemic anticoagulation (with heparin) is used to prevent clotting of the hemodialysis circuit. Dialysis membranes are classified as conventional or standard, high efficiency, and high flux. Conventional dialyzers, mostly made of cuprophane or cellulose acetate, have small pores that limit clearance to relatively small molecules (size ≤ 500 daltons) such as urea and creatinine. High-efficiency membranes have large surface areas and thus have a greater ability to remove water, urea, and other small molecules from the blood. High-flux membranes have large pores that are capable of removing high-molecular-weight substances, such as β2-microglobulin, and certain drugs, such as vancomycin ***(Daugirdas et al., 2001a; Schulman, 2002)***.

The primary reason to use high-efficiency and/or high-flux membranes is that clearance of both low- and high molecular- weight substances is much greater than with the conventional membranes, so treatment times can be shorter. The use of high-flux and high-efficiency dialysis increased significantly in the United States during the 1990s. High-efficiency and high-flux dialysis require blood flow rates greater than 400 mL/min, dialysate flow rates greater than 500 mL/min, and the use of strict controls on the rate of fluid removal. Typically these dialyzers are composed of polysulfone, polymethylmethacrylate, polyamide, cellulose triacetate, and polyacrylonitrile ***(Daugirdas et al., 2001b)***.