EVALUATION OF TIME TO ACHIEVE DRY WEIGHT USING BODY COMPOSITION MONITOR, HYPERTENSION MANAGEMENT AND PREVALENCE OF DEPRESSION AMONG HEMODIALYSIS PATIENTS IN KELANTAN MALAYSIA

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2018

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by

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Thesis submitted in fulfillment of the requirements for the degree of Doctor of Philosophy

December 2018

DEDICATION

I dedicate this thesis to my beloved parents and wife for all their love, patience, kindness and support.

ACKNOWLEDGEMENT

First, I would like to express my humblest thanks to Allah Almighty for His endless blessings and help to complete this research. I am greatly indebted to all those who have contributed for completion of this work.

My deep gratitude goes to my main supervisor Dr. Amer Hayat Khan, who expertly guided me throughout my PhD and his unwavering enthusiasm for clinical pharmacy kept me constantly engaged with my research. I would like to express special thanks and sincere appreciation to my co-supervisors, Prof. Dr. Syed Azhar Syed Sulaiman and Assoc. Prof. Dr. Azreen Syazril Adnan for their wonderful suggestions, insightful comments along the way and for making me a part of chronic kidney resource center. My special acknowledgement goes to staff members of chronic kidney resource center at Hospital Universiti Sains Malaysia and its associated dialysis centers for their generosity and collaboration during data collection. I am also grateful to all the patients for their participation in the study. I want to acknowledge the Institute of Postgraduate Studies (IPS) at Universiti Sains Malaysia, who awarded me USM Fellowship Award throughout my candidature period.

Last but not the least, I would like to thank to my family for unwavering support and unconditional love. To my parents and brothers, I wouldn’t have come this far without them. To my beloved wife, who have been there for me all the time. I truly appreciate their love, patience and all the sacrifices they made supporting me and cheering me up during this long challenging journey.

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LIST OF ABBREVIATIONS

ADHF	Acute decompensated heart failure
ACE	Angiotensin-converting enzyme
ARBs	Angiotensin receptor blockers
ACE inhibitors	Angiotensin converting enzyme inhibitors
AV fistula	Arteriovenous fistula
BIS	Bioimpedance spectroscopy
BCM	Body composition monitor
BMI	Body mass index
BP	Blood pressure
BNP	Brain natriuretic peptide
CCBs	Calcium channel blockers
CVD	Cardiovascular diseases
CVA	Cerebrovascular accident
CKD	Chronic kidney disease
CKD-MBD	chronic kidney disease associated mineral and bone disorder
CHF	Congestive heart failure
CAD	Coronary artery disease
CG	Cockroft Gault
CRP	C-reactive protein
DM	Diabetes Mellitus
DW	Dry weight
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
ECW	Extracellular water
EPO	Erythropoietin
FO	Fluid overload
GFR	Glomerular filtration rate
HADS	Hospital anxiety and depression scale
HUSM	Hospital Universiti Sains Malaysia
HD	Hemodialysis

HRQoL	Health Related Quality of Life
ICW	Intracellular water
KDIGO	Kidney disease improving global Outcomes
LVH	Left ventricular hypertrophy
MICS	malnutrition-inflammation complex syndrome
MRDRD	Modification of Diet in renal disease
NKF	National kidney foundation
NKF-KDOQI	National kidney foundation-Kidney Disease Outcomes Quality Initiative
NGO's	Non-governmental organizations
NSAIDS	Non-steroidal anti-inflammatory drugs
NT-pro BNP	N-terminal pro-brain natriuretic peptide
OH	Over hydration
PC	Peritoneal cavity
PD	Peritoneal dialysis
PgE2	Prostaglandin
RAAS	Renin angiotensin aldosterone system
SBP	Systolic blood pressure
TBW	Total body water
US	United states
USRD	United States Renal Data System
WHO	World health organization

PENILAIAN MASA UNTUK MENCAPAI BERAT BADAN KERING MENGGUNAKAN PEMANTAUAN KOMPOSISI BADAN, PENGURUSANHIPERTENSI DAN PREVALEN DALAM KALANGAN PESAKIT HEMODIALISIS DI KELANTAN MALAYSIA

ABSTRAK

Hampir 60-90% pesakit hemodialisis (HD) mempunyai hipertensi. Pencapaian dan pengekalan berat kering merupakan strategi yang berkesan dalam mengawal dan mengekalkan normotensi dalam kalangan pesakit hipertensi yang menerima terapi HD. Pemonitoran komposisi badan (BCM) membantu dalam penganggaran status penghidratan pesakit dan berat kering dengan lebih tepat. Bagi tujuan ini, kajian ini menentukan masa pesakit mencapai berat kering selepas dialisis dengan menggunakan spektroskopi bioimpedan (BIS) di Hospital Universiti Sains Malaysia (HUSM), iaitu sebuah hospital penjagaan lestari beserta dengan sekumpulan pusat rawatan swasta di Kelantan, Malaysia. Dalam kajian prospektif, sejumlah 220 pesakit HD dinilai tahap lebihan bendalir dengan menggunakan pemonitoran komposisi badan Fresenius (BCM). Pengukuran BCM diambil sebanyak dua kali iaitu pada 30 dan 45 minit selepas pemeriksaan. Daripada jumlah 220 pesakit,120 (54.5%) mencapai keadaan euvolemik selepas 30 minit, manakala 25 orang (11.4%) selepas 45 minit. Dalam analisis multivariat, akses vaskular selain fistula arteriovenous (AVF) (OR = 0.286, nilai p = 0.049) dan penyakit kardiovaskular (OR = 0.384, nilai p = 0.026) mempunyai hubung kait negatif manakala penerimaan terapi hemodialisis di HUSM (OR = 2.705, nilai p = 0.008) mempunyai hubung kait positif yang juga signifikan pada keadaan euvolemik dicapai dalam masa 30 minit. Tambahan lagi, kami menilai kawalan hipertensi dan faktor-faktor yang mempengaruhi kawalan hipertensi dalam kalangan pesakit hemodialisis hipertensi euvolemik. Kajian ini mengambil kira data 145 pesakit hemodialisis euvolemik. Pada lawatan asas, purata tekanan sistolik dan diastolik pra-dialisis peserta kajian adalah masing-masing 161.2 ± 24 dan 79.21 ± 11.8 mmHg manakala 30 (20.6%) pesakit berada pada tekanan darah pradialisis sasaran. Pada akhir pemeriksaan selepas enam bulan, purata tekanan darah pra-dialisis sistolik dan diastolik pesakit adalah 154.6 ± 18.3 dan 79.2 ± 11.8 mm Hg manakala 42 (28.9%) berada pada tekanan darah pra-dialisis. Sasaran analisis multivariat, penggunaan ubat perencat saluran kalsium (CCB) adalah satu-satunya pemboleh ubah yang mempunyai persamaan statistik yang signifikan dengan hipertensi terkawal pradialisis pada awalan (OR = 7.530, p-value = 0.001) dan akhir (OR = 8.988, nilai <0.001) lawatan. Bagi enilaian prevalens dan peramal kemurungan dalam kalangan pesakit HD, kajian susulan prospektif dijalankan. Sejumlah 220 orang pesakit telah direkrut dalam kajian yang layak dan lengkap pada lawatan asas. Seterusnya, 216 dan 213 pesakit masing-masing menyelesaikan soal selidik pada kedua dan akhir susulan. Prevalen kemurungan dalam kalangan pesakit di peringkat awal, pada kunjungan ke-2 dan lawatan terakhir masing-masing adalah 71.3%, 78.2% dan 84.9%. Rawatan yang diberikan kepada pesakit di pusat-pusat HD di bawah badan NGO (OR = 0.347, p-value = 0.039) mempunyai persamaan yang signifikan dengan prevalen kemurungan pada lawatan akhir. Sebagai kesimpulan, kajian ini menunjukkan bahawa penilaian status isipadu pada 45 minit selepas pemeriksaan semua pesakit atau ke atas individu yang mempunyai faktor risiko yang dikenal pasti tidak mengalami euvolemia pada 30 minit akan memberikan penilaian yang agak tepat bagi kebanyakan pesakit. Hal ini dapat membantu mengelakkan berlakunya anggaran yang berlebihan tentang hipertensi, menggalakkan penggunaan ubat anti hipertensi, secara rasional mengurangkan kesan buruk dan meningkatkan kualiti hidup pesakit. Hubung kait

positif yang diperhatikan di antara CCB dan hipertensi terkawal menunjukkan bahawa CCB adalah ubat antihipertensi yang berkesan dalam mengawal hipertensi dalam kalangan pesakit euvolemik HD. Disamping itu, kemurungan adalah lazim dalam peserta kajian semasa. Perkaitan signifikan secara statistik dicerap antara kemurungan dan HD di pusat-pusat NGO membuktikan kepuasan pesakit dan pengurusan kemurungan yang lebih baik di pusat-pusat tersebut.

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ABSTRACT

Almost 60-90 % hemodialysis (HD) patients are hypertensive. Achieving and maintaining dry weight appears to be an effective strategy for controlling and maintaining normotension among hypertensive patients on HD therapy. Body composition monitor (BCM) helps estimate patient hydration status and dry weight accurately. For this purpose, the present study aimed to determine the time at which the majority of patients achieve postdialysis dry weight using bioimpedance spectroscopy (BIS) at Hospital Universiti Sains Malaysia (HUSM), a tertiary care hospital and a group of private centers outside the hospital in Kelantan, Malaysia. A total of 220 HD patients were prospectively assessed for fluid overload using the Fresenius body composition monitor (BCM). BCM readings were taken at 30 and 45 minutes postdialysis. Among the 220 patients included in this study, 120 (54.5%) achieved a euvolemic state at 30 minutes, and 25 (11.4%) achieved it at 45 minutes according to the BCM. In the multivariate analysis, vascular access other than arteriovenous fistula (AVF) (OR=0.286, p value=0.049) and cardiovascular disease (OR=0.384, p value=0.026) had a statistically significant negative association and receiving hemodialysis therapy at HUSM (OR=2.705, p value=0.008) had a statistically significant positive association with achieving a euvolemic state at 30 minutes. Moreover, we evaluated hypertension control and factors influencing hypertension control among euvolemic hypertensive hemodialysis patients. This study included 145 euvolemic hemodialysis patients. On baseline visit, the mean pre-dialysis systolic and diastolic BP (mmHg) of study participants was 161.2 ± 24. and 79.21 ± 11.8 respectively, and 30 (20.6%) patients were on pre-dialysis goal BP. At the end of the 6-months follow-up, the mean pre-dialysis systolic BP and diastolic BP (mmHg) of the patients was 154.6 ±18.3 and 79.2 ±11.8 respectively, and 42 (28.9%) were on pre-dialysis goal BP. In multivariate analysis, the use of calcium channel blockers (CCB) was the only variable which had statistically significant association with pre-dialysis controlled hypertension at baseline (OR= 7.530, p-value= 0.001) and final (OR= 8.988, p-value <0.001) visits. For the assessment of prevalence and predictors of depression among HD patients, prospective follow-up study was conducted. A total of 220 patients were judged eligible and completed questionnaire at the baseline visit. Subsequently, 216 and 213 patients completed questionnaire on second and final follow up respectively. The prevalence of depression among patients at baseline, 2nd visit and final visit was 71.3%, 78.2% and 84.9% respectively. Treatment given to patients at NGO's running HD centers (OR= 0.347, p-value= 0.039) had statistically significant association with prevalence of depression at final visit. In conclusion, this study suggests that assessing volume status at 45 minutes postdialysis will provide a relatively accurate assessment for the majority of patients, will help to prevent the overestimation of hypertension, encourage the rational use of antihypertensive drugs, reduce adverse effects and improve patient quality of life. The positive association observed between CCBs and controlled hypertension suggests that CCBs are effective antihypertensive drugs in the management of hypertension among euvolemic HD patients. Statistically significant association observed between depression and HD at NGO's running centers signifies patients' satisfaction and better depression management practices at these centers.

CHAPTER 1
INTRODUCTION

1.1 Background

The excessive mortality of hemodialysis (HD) patients due to cardiovascular events is related mostly to hypertension and cardiac damage (Hur *et al.*, 2013). Various studies have shown that strict volume strategy is associated with decrease blood pressure (BP) without drugs, causes regression of left ventricular hypertrophy (LVH) and prolongs survival in hemodialysis patients (Bernard Charra & Chazot, 2003; Ozkahya *et al.*, 1998). In clinical practice, two procedures are usually carried out for fluid management in dialysis patients that is subjective clinical assessment and the probing of dry weight procedure (Canaud & Lertdumrongluk, 2012). The concept of “dry weight” which has a history of more than half a century now, is routinely used in current practice in virtually all HD centers worldwide. However, the best way to assess fluid status and dry weight is still an unsolved issue (Onofriescu *et al.*, 2012). Dry weight in dialysis patients is a variable entity which implies a state of near euvolemia (Raza *et al.*, 2018). Tracking the optimal dry weight among dialysis patients requires enough time and skills of physicians, nursing staff and adequate therapy. New noninvasive technologies such as bioimpedence spectroscopy (BIS) can assess fluid status in a more accurate way (Velasco *et al.*, 2012). Currently there is an uncertainty in determining the optimal time for BP measurement and BP targets among HD patients (Onofriescu *et al.*, 2014). Bioimpedence spectroscopy also has been used successfully to guide HD patients toward normohydration and better BP control (Machek, Jirka, Moissl, Chamney, & Wabel, 2009).

Hypertension is very common, not an easy task to diagnose it properly and usually uncontrolled among HD patients. There have been always controversies regarding the diagnosis and treatment of hypertension in this specific population (Agarwal *et al.*, 2014). It is still challenging to treat hypertension due to various unsolved problems and procedures for the management of hypertension in patients on dialysis (Taniyama, 2016). High pre-dialysis and post-dialysis BP recordings demonstrate a U-shaped association with mortality among patients on dialysis (Zager *et al.*, 1998). Instead of initiating or intensifying antihypertensive treatment, strict sodium and volume control is the best strategy for the management of hypertension among hemodialysis patients. Antihypertensive treatment is only recommended when patients already achieving normal volume status but still in hypertensive state, except diuretics all other major antihypertensive classes are considered effective in the treatment of hypertension in dialysis patients (Georgianos & Agarwal, 2016).

Initiation of dialysis therapy causes surprising changes in the life of dialysis patients which leads to physical and mental stress. This is a reason why dialysis patients develop neuropsychiatric complications (Teles *et al.*, 2014). Among these complications, depression ranked first due to its high prevalence and as it is associated with poor quality of life of patients and increased mortality. The prevalence of depression is much higher in dialysis patients as compared to general population and patients with other chronic diseases (Jiang *et al.*, 2001; Kessler *et al.*, 2003).

As volume overload is the major risk factor for hypertension, little is known about the optimal time of dry weight achievement and euvolemic state in hemodialysis patients while employing post-dialysis BCM sessions. Moreover, almost no contribution is made towards hypertension control and risk factors associated with hypertension control in euvolemic hypertensive hemodialysis patients. Despite the high prevalence of depression, predictors of depression and its impact on the life of hemodialysis patients has remained a neglected area. Therefore, the current study aimed to determine the optimal time of post-dialysis dry weight achievement by using bioimpedence technology, hypertension control and factors associated with hypertension control and prevalence and predictors of depression among hemodialysis patients.

1.2 Dry weight

In hemodialysis patients, the dry weight is defined as "the lowest tolerated postdialysis weight achieved via gradual change in postdialysis weight at which there are minimal signs or symptoms of hypovolemia or hypervolemia" (Agarwal & Weir, 2010). After achieving dry weight, the extracellular volume becomes normal (Charra *et al.*, 1996). Incorrect assessments of dry weight are very risky as it either leads to chronic hypervolemia or chronic hypovolemia. Fluid overload assessment is quite difficult. Fluid assessment may be conducted by using different ways in routine clinical settings such as on the basis of physical signs of edema, high blood pressure (BP) and cardiovascular (CV) complications. In this connection, physical signs of edema may provide with rough estimates of excessive extracellular volume. Moreover, it requires retention of several liters of water before the appearance and visibility of physical signs of edema (Devolder, Verleysen, Vijt, Vanholder, & Van Biesen, 2010; van Dijk *et al.*, 2013). In addition to the above referred methods, ultrasonic evaluation of diameter of the inferior vena cava is another technique employed for assessment of fluid status. However, there could be a possibility of inter-patient and inter-operator variability in this case. Apart from this, several other biomarkers techniques may also be used for assessment of changes in fluid status such as "brain natriuretic peptide (BNP)" and "N-terminal pro-brain natriuretic peptide (NT-pro BNP)". However, both of these are usually induced by presence of CV disease and it has been reported that these may also buildup in patients suffering from chronic kidney disease (CKD), making the execution of these methods unsuitable to assess the status of fluids (Yilmaz *et al.*, 2014). More recently, another technique *viz.* bio-impedance spectroscopy has demonstrated better results regarding successful and fruitful assessment of fluid status and in estimation of dry weight among HD patients (Earthman, Traughber, Dobratz, & Howell, 2007).

The term “Dry weight” was first introduced by Thomson in 1967 (Thomson, Waterhouse, McDonald, & Friedman, 1967). In previously conducted research achieving dry weight in HD patients has been widely associated with better prognosis and improved survival rates (Agarwal, Alborzi, Satyan, & Light, 2009). On the other hand, the under- and overestimation of dry weight in HD patients have been associated with unwanted consequences of adverse events and cardiovascular morbidity and mortality (Agarwal, 2005; McIntyre *et al.*, 2008; Shoji, Tsubakihara, Fujii, & Imai, 2004). Therefore, establishing the ideal weight and maintaining the fluid balance in these patients has always remained a priority for nephrologists and an ongoing goal of clinical research. The previously published research has reported BCM as the most accurate, reliable and valid technique for assessing the HD patients’ status and deciding about achieving the dry weight. In a study, BCM was used for the purpose of guiding the HD patients towards normohydration. The findings of the study reported that BCM guided 2L fluid decrease in hyperhydrated patients led to no intradialytic symptoms and a significant systolic BP reduction of 25 mm Hg. Similarly, in the same study, BCM guided 1.3 L increase in patients of adverse events group resulted in a remarkable 73% reduction in intradialytic symptoms without affecting BP level (Moissl *et al.*, 2013). Similar positive results regarding the accuracy and validity of BCM in assessing hydration status in HD and PD patients have been reported from

Belgium, Thailand and Italy (Chongthanakorn, Tiranathanagul, Susantitaphong, Praditpornsilpa, & Eiam-Ong, 2009; Crepaldi *et al.*, 2009; Devolder *et al.*, 2010).

1.2.1 Benefits of probing dry weight

Exploring dry weight has been strongly supported by observational investigations. A study reported that 35 out of 40 patients exhibited normotensive status after accomplishment of the dry weight (Charra *et al.*, 1996). In another published report related to "control of left ventricular mass among HD patients", Kayikcioglu *et al.* have described the visible advantages of non-pharmacological treatment over the pharmacologic treatment (Kayikcioglu *et al.*, 2008). In this regard a case control study may be presented wherein results obtained from different patients treated at two different centers were compared. In this comparative study, non-pharmacological methods such as salt restriction and dry weight reduction were used for patient treatment at one center; while pharmacological method such as antihypertensive based therapy for managing of hypertension was employed at the other center. It was observed that the former center using "dry weight and salt restriction" (non-pharmacological) as a top priority for patient treatment demonstrated better "diastolic and systolic left ventricular function", lower usage of antihypertensive drugs, fewer episodes of intradialytic hypotension, lower interdialytic function and lower left ventricular mass. These observations provide useful clinical information and suggest that in-depth investigation of dry weight is a significantly useful strategy with better clinical outcomes in contrast to the antihypertensive based drugs strategy. Although the findings from a case control study may not always be conclusively precise, yet the results obtained from such a study do favor the advantages of 'non-pharmacological' against the 'pharmacological therapy' to effectively manage hypertension in patients with end stage renal disease (ESRD) (Kayikcioglu *et al.*, 2008).

1.2.2 Assessment of dry weight

In a study conducted by Agarwal and his co-authors, it was found that some of the procedures for dry weight assessment like diameter of 'inferior vena cava', volume of plasma & inflammation markers and monitoring of blood volume were not the essential determinants of edema (Agarwal, Andersen, & Pratt, 2008). Dry weight assessment and its achievement is considered to be an iterative process usually associated with some painful intradialytic symptoms like hypotension, dizziness, cramps etc. Due to these symptoms, various interventions are recommended including discontinuation of ultrafiltration, premature cessation of dialysis, patient's head-down positioning or administration of saline. It has been reported that the practice of keeping a patient in head down position gives uncertain results and it may not essentially control BP of such patients (Bridges & Jarquin-Valdivia, 2005); however, it has been observed that ventricular filling pressure can be effectively raised by passively raising the legs of the patient without lowering the head (Jabot, Teboul, Richard, & Monnet, 2009). The dry weight can be accomplished effectively by adequate ultrafiltration in dialysis sessions and by regular monitoring and comparison with previously recorded dry weight of the patients. Having mentioned all the above referred facts, it is still valid to state that a BCM employing the principle of bioimpedence technology can be used more successfully for obtaining the most accurate and precise patient's dry weight estimation.

1.3 Bioimpedence spectroscopy

Bioimpedence spectroscopy is a uniquely modern method employed to assess distribution of fluid in either of the healthy and/or diseased population. BCM using bioimpedence technology provides a validated technique after its intensive validation using various gold standards in normal population or in HD patients (Devolder *et al.*, 2010; Wabel, Chamney, Moissl, & Jirka, 2009). However, few investigations could come with successful validation with respect to non-dialysis-dependent chronic kidney disease (NDD-CKD) population.

“BIS is a non-invasive trouble-free technique which can be used for the determination of body fluids amount and for body composition with respect to lean tissue and fat tissue mass”. This technique may be used for measuring the “total body water (TBW)” and also for separation between “extracellular & intracellular water (ECW & ICW)” (Earthman, Traughber, Dobratz, & Howell, 2007). ‘TBW’ represents the simple sum of ECW & ICW, where ECW is comprised of plasma water, interstitial water and the trans-cellular water, while the ICW consists of intra-cellular water with the cells being protected by cell membrane (Ferrario *et al.*, 2014).

The whole-body impedance spectroscopy method uses current with multi-frequency (5-1000 kHz) and low amplitude. In case of low frequency, the above referred current can only pass through extracellular water because of its inability to pass through the cell membranes while the current passes at high frequency through TBW (Hung *et al.*, 2015; Tsai *et al.*, 2014). According to basic principle of BIS, when multi-frequency current is applied throughout the body, resistance is offered by every compartment of the body in response to applied current which is directly proportional to TBW and electrolytes of that compartment. Lean tissue is considered as an excellent conductor of electric current because of having water and electrolytes in large quantities with a little resistance to current flow. In contrast, bones & fats have smaller amount of water and electrolytes, so they offer high resistance to current flow (Mialich, Sicchieri, & Junior, 2014).

It has been reported that fluid overload (FO) value or over hydration (OH) can best be defined in terms of ECW and is generally expressed in liters (Ferrario *et al.*, 2014). “Over hydration (OH) represents the extracellular water (ECW) content in those tissues which may be predicted by the help of physiological models under normal conditions. Thus, the values of OH obtained with the use of BCM can be compared with the values obtained from general population” (Hung *et al.*, 2015).

1.3.1 Clinical uses

“Bioimpedence spectroscopy is a unique and modern tool generally required and used by health care skilled persons for determination of patient’s hydration status and for differentiation between ECW and ICW”. Nutritionist use this technique for various purposes in clinics as well as in weight management centers. This device is quite helpful in the management of hypertension and maintaining euvolemia according to patient needs as the device is perfect for appropriate assessment of total body water and BP. The most important use of BIS is in hemodialysis patients. By the help of BIS, we can determine urea distribution volume “V” in dialysis patients that is the volume of fluid which should be removed during the dialysis process (Mialich *et al.*, 2014).

1.3.2 Limitations

For the last several years, relevant experts have extensively validated the BIS based body composition in healthy as well as in diseased population. Despite many advantages of the technique like easy handling, providing quick results and easy interpretations there are still some limitations associated with this technique. Due to difficulty in attachment of electrodes to the hands and feet of the patient, BIS may not conveniently have used in many cases including, but not limited to, patients with amputations or pacemakers, pregnant females and patient with various skin infections.

In some other conditions such as retention of water (Congestive cardiac failure and liver cirrhosis) and in cases of water-electrolyte imbalance, the results will not be that much accurate. Heavy meals, dehydration, menstrual cycle and intense physical exercise are among the other factors which can affect the accuracy of results (Charra, 2007).

1.4 Chronic kidney disease

1.4.1 Background

The heterogeneous group of disorders which affect the structure and functions of kidney are referred to as chronic kidney disease (CKD) (Levey *et al.*, 2003). Keeping in view the increasingly large number of kidney failure cases and, more importantly, the alarmingly high number of patients suffering from kidney-cum-cardiovascular diseases which undoubtedly contribute in enhancing premature deaths even before reaching the condition of kidney failure, a global initiative to address such issues would not only be considered as rational rather 'a must be done activity' (Levey *et al.*, 2005). In this connection, many efforts have been made for improvement of the relevant outcomes and also for the betterment of CKD patients care in order to stop them reaching toward the sever condition of kidney failure. However, the desired objectives were not achieved, perceivably due to reasons including paucity of data obtained from clinical trials in the area of nephrology and also due to lack of any valid definition capable enough to agreeably categorize CKD patients in terms of severity. Therefore, it is being felt and does merit to properly define disease severity of CKD patients and to classify, in a candid manner, different levels of risk in order to ascertain suitable treatment of such patients and to help prevent continuation and/or advancement of the disease towards renal failure (Levin *et al.*, 2010).

1.4.2 Definition

"According to the National Kidney Foundations' (NKF) clinical practice guidelines produced through the NKF Kidney Disease Outcomes Quality Initiative (NKF KDOQI), CKD is defined as kidney damage for ≥ 3months, as defined by structural or functional abnormalities of the kidney, with or without decrease glomerular filtration rate (GFR), manifest by either pathological abnormalities or marker of kidney damage, including abnormalities in composition of blood or urine or abnormalities in imaging test or "GFR < 60 ml/min/1.73m^2 for ≥ 3 months, with or without kidney damage" (Levey *et al.*, 2002).

1.4.3 Classification / Staging of kidney disease

NKF-KDOQI proposed the following five stages of CKD.

Table 1.1 Classification of Chronic kidney disease

CKD staging	**GFR(ml/min/1.73m^2)**
1	≥90
2	60-89
3	30-59
4	15-29
5	<15

Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (Levey et al., 2002).

Stage 1 shows the least complicated stage while the end stage renal disease with significant loss of renal function is depicted in stage 5.

After its introduction in 2002, several suggestions have been considered to modify the kidney staging system. In this connection, following three main modifications were proposed in International Controversy Conference 2009 (Levin *et al.*, 2010):

1. The known cause of disease should be added to CKD staging as it plays a prime role in prediction of outcomes leading towards making decisions to select suitable treatment
2. The "CKD stage 3 (GFR 30 – 59 ml/min/1.73m^2)" should be divided into two sub-stages *viz.* 3a (45 < eGFR < 59) and 3b (30 < eGFR < 44)
3. Albuminuria should also be added to CKD staging in order to assess disease severity

Keeping in view the above referred recommendations, "the Kidney Disease Improving Global Outcomes (KDIGO) suggested a cause-GFR-albuminuria (CGA) categorization of CKD which is summarized as under".

Table 1.2 KDIGO classification of chronic kidney disease

GFR category	**GFR(ml/min/1.73m^2)**	**Level of kidney function**
G1	≥90	Normal or high
G2	60-89	Mild decreased
G3a	45-59	Mild to moderate decreased
G3b	30-44	Moderate to severe decreased
G4	15-29	Severe decreased
G5	≤15	Kidney failure
Albuminuria	AER (mg/24 hour)	Level
A1	<30	Normal to mild increased
A2	30-300	Moderate increased
A3	>300	Severe increased
GFR: glomerular filtration rate; AER: albumin excretion rate		

Improving global outcomes controversies conference (Levin et al., 2010).

1.5 End stage renal disease

"It is a condition where GFR levels are less than 15 ml/min/1.73m^2 and is also accompanied with signs and symptoms of uremia". ESRD-patients require the therapy of renal replacement that may be performed by the process of dialysis or through transplant (Levey *et al.*, 2002).

The process of protein metabolism can produce creatinine as one of its bi-product. As and when kidneys do not work properly and clearance from kidneys is reduced, the normal levels of creatinine, urea and uric acid would be elevated (Cockcroft & Gault, 1976). Depending on kidney function, patients of stage 4 may also need dialysis. Basically, dialysis acts like artificial kidneys eliminating waste products and excessive electrolytes from the blood. The two types of dialysis commonly in practice are:

1. Hemodialysis

2. Peritoneal dialysis

In hemodialysis, blood filtration takes place through specific dialysis filters and solution. Before starting HD for any patient, it is necessary to first create a vascular access that may help in drawing the blood into the dialysis machine in order to filter it through the membrane filters, and the dialysis solution is pushed through a pump onto the alternate side of the membrane filter to aid the process by ion exchange action. In this fashion, based on concentration gradient, waste products are drawn to the dialysis solution. After this, the waste products accumulated in the machine are pumped out and the blood is pumped back into patient's body. Completion of this procedure usually takes about 4 hours (Saran *et al.*, 2017).

However, the procedure of peritoneal dialysis (PD) is different from that of the HD. In PD a catheter is inserted in peritoneal cavity (PC) of the patient instead of vascular access creation. The dialysis solution used for filling of the peritoneal cavity is the same as used in case of HD and the waste products it is removed periodically (Wiggins, Johnson, Craig, & Strippoli, 2007).

1.6 Prevalence of end stage renal disease

The highest prevalent countries with respect to ESRD include Taiwan, Japan, Mexico, US and Belgium. According to mortality data of 2007 and based on comparable treatment modalities, the risk of mortality in ESRD patients in USA are 15% higher than those in Europe and 33% higher when compared to patients in Japan (Masereeuw & Stamatialis, 2017).

According to the report of ‘US Renal Data System’, not less than 660,000 patients in USA are treated for renal failure every year. About 468,000 out of total ESRD patients happen to be use dialysis therapy while more than 193,000 have to opt for kidney transplant. According to 2013 data report, about 117,000 Americans suffered from kidney failure cases, 57.3% being male and 42.69% female patients. A total of 44.3% patients belonged to age group of 45 – 64 years. The primary causes for ESRD remained diabetes (37.4 %) and hypertension (25.2%) (Saran *et al.*, 2017).

According to “global burden of disease report 2010”, in the list of death cases chronic kidney disease ranked 27th in 1990 and 18th in 2010. It is observed that worldwide > 2 million ESRD patients receive dialysis or kidney transplant (Couser, Remuzzi, Mendis, & Tonelli, 2011). In countries with middle income, ESRD treatment remains a financial burden over the needy patients. Many of them cannot afford it financially and consequently > a million patients die every year because of non-treatment of the kidney failure complication. Worldwide, the estimated share of Europe is 13% in connection to prevalence of ESRD. Portugal, Germany Cyprus, Spain and Italy are among the countries with highest prevalence. In Europe, among 552,000 patients, 575 are on HD, 5% with PD and 39% are alive after kidney transplant. Data show that in Europe kidney transplant is growing at faster rates with an average of 3% increase/year (Couser *et al.*, 2011). According to a published report, in England the CKD associated cost is higher than the combined cost of lung, colon, skin and breast cancer, where the CKD related cost is estimated to become as high as $ 12 billion by 2020. Similarly, in Uruguay, annual cost of HD therapy is reportedly $ 23 million that is equal to almost 30% of total budget allocated for all the specialized therapies. Finally, China has decided to spend about $558 billion on heart diseases and kidney failure cases over next decade (Nasri, 2014).

1.7 Prevalence of end stage renal disease in Malaysia

In Malaysia, the prevalence report of CKD demonstrated to be 4.16, 2.05, 2.26 and 0.24% for stage 1, 2, 3 and 4, respectively while ESRD prevalence was reported as 0.36% (Hooi *et al.*, 2013). According to the 23rd report of the Malaysian dialysis and transplant registry (MDTR, 2015), a linear increase prevailed in the number of HD patients over 10 years where in 2006 the reported dialysis cases were 3710 which have been increased to 6479 cases in 2015. It has been reported that in Malaysia the rate of kidney transplant cases decreased to about 50% over last decade, probably due to easy and convenient availability of dialysis therapy; and it was estimated to be about 3 per million population (pmp) in the latest MDTR report (MDTR, 2015). According to this published report, there were 1118 new peritoneal dialysis cases with acceptance rate of 37 pmp. In 2015, the total number of HD and PD patients reached to 33,456 and 3727, respectively that exhibit the respective prevalence rate of 1097 and 122 pmp.

Moreover, by year 2015, the rate of treatment of dialysis patients surpassed 200/million population throughout Malaysian states except for Perlis and Sabah (MDTR, 2015).

1.8 Complications associated with end stage renal disease

Healthy kidneys have various important functions including removal of waste products, regulate hypertension, maintenance of electrolyte imbalances, maintain body fluids, production of calcitriol and production of urine. Moreover, Kidneys also produce erythropoietin which is responsible for red blood cells formation. When kidneys become impaired the equilibrium is disturbed which is maintained by normal kidneys resulting in variety of disorders. Common complications associated with ESRD are described as under:

1.8.1 Cardiovascular disease as a complication of end stage renal disease

The most frequent complication associated with ESRD is cardiovascular disease. It is reported that annual mortality rate is 44% associated with ESRD (Herzog, Ma, & Collins, 1998). Higher mortality rates are reported in HD patients as compared to the general population with respect to cardiovascular events despite stratification for gender, ethnicity or even age group. The incidence of cardiovascular mortality is 500 times more in young dialysis patients as compared to cardiovascular patients in general population (Foley, Parfrey, & Sarnak, 1998). Using the US renal database system, Herzog *et al.* studied 34,189 HD patients and found that poor prognosis prevailed among such patients who were suffering from acute infarction. Their published results showed that cardiovascular mortality rates were 51.8 and 70.2 % after 2 and 5 years, respectively (Herzog *et al.*, 1998).

It merits a mention that prevalence of cardiovascular events happened to constantly increase not only with the ESRD but also among the patients suffering from chronic kidney diseases. As glomerular filtration declines, elevation in prevalence of LVH would be observed and it is reported that clinical evidences related to ischemic heart disease were found in almost 30% of patients reaching ESRD. Moreover, it is noteworthy that patients having more risk to die due to cardiovascular events with reduced glomerular filtration as compared to progression towards ESRD (Shulman *et al.*, 1989).

The relationship found between cardiovascular events and ESRD revealed to include common pathological links which further depend upon the prevalence of traditional and nontraditional reasons; where such traditional factors could be anemia, hypertension, dyslipidemia, electrolytes imbalances and acid-base or mineral related complications, whereas inflammation problems, oxidative stress and fluid overload may be included among the non-conventional factors (Shlipak *et al.*, 2001). CKD-Mineral and Bone Disorder (CKD-MBD) leads to increase in parathyroid hormone which actually increases the risk of cardiac mortality and also contributes to develop left ventricular hypertrophy like phenomenon, mainly due to presence of parathyroid receptors in the heart (Bhuriya, Li, Chen, McCullough, & Bakris, 2009). Additionally, parathyroid hormone can also cause atherosclerosis and increased vascular tone that may further lead towards hypertension, an important risk factor for cardiovascular diseases. Pro-inflammatory cytokines also releases due to malnutrition that may aggravate the existing inflammation and may also accelerate arthrosclerosis (Pecoits-Filho, Lindholm, & Stenvinkel, 2002). Fluid overload, too, is a main cause of hypertension in ESRD patients which influences vascular functions and may lead towards left ventricular hypertrophy, atherosclerosis and/or arterial stiffness.

Interestingly, "Reverse causation," wherein the CKD is considered as a risk factor complication such as CVD and *vice versa*, is another interpretation for possible association between the two diseases (Elsayed *et al.*, 2007). Such an association existing between CKD and CVD is known as "cardio-renal syndrome" which may be defined as "the disorder of kidney or heart in which certain acute and/or chronic disorder present in one organ may induce an acute or chronic disorder into the other organ" (House *et al.*, 2010).

1.8.2 Hypertension as complication of end stage renal disease

Usually, the ESRD patients suffer from hypertension, and its prevalence is up to 90% in such patients. As the kidney function declines, the prevalence of CKD related hypertension increases linearly. Among the HD patient's pathogenesis of hypertension is very complicated and has not been perfectly explored yet. However, based on the known published research work it may be stated that, *inter alia*, hypervolemic conditions, renin angiotensin receptor blockers, enhanced sympathetic activity and altered endothelial cell functions could be the possible contributors out of so many relevant expected reasons (Ekart, Bevc, & Hojs, 2011)

1.8.2(a) Volume overload induced hypertension

Hemodialysis procedure replaced the excretory function of kidneys in hemodialysis patients. Absorption of salt and water is same between normal people and hemodialysis patients however their excretion requires hemodialysis procedure. In between each dialysis session, 1-3 liters of extracellular water is gained. These constant fluctuations lead to high blood pressure in hemodialysis patients (Doulton & MacGregor, 2004). Fluid intake is quantitative dependent on thirst of an individual which is turn is dependent on osmolality (Tomson, 2001) and that sodium concentration may determine the osmolality. It may be said that Plasma osmolality dependent upon the intake of dietary salt and on the net amount of sodium gained or lost during the process of dialysis. Excretion of sodium from kidney usually takes place within an hour (He, Markandu, & MacGregor, 2001). Almost similar mechanism is encountered in cases of kidney failure patient's however such patients are unable to excrete sodium due to diseased kidneys, retention of sodium in plasma for longer than normal time occurs which causes induction of thirst in such individuals. Induction of thirst causes a higher intake of water and/or other fluids that culminate in overloading the volume which in turn results in higher BP observed among HD patients (Singer *et al.*, 1998). Conclusively, reducing intake of salt is absolutely essential in on order to reduce thirst as well as interdialytic weight gains.

Volume overload is the result of higher intake of fluid and retention of sodium in the body and this in turn affects the vascular system by non-hemodynamic influences. HD patients are at greater risk of cardiac failure when they begin dialysis with low pre-dialysis blood pressure, this may lead towards poor prognosis of HD patients due to slower removal of fluid. On further aggregation and analysis of this scenario, it may be said that HD patients usually face diastolic dysfunction. In such HD patients, a little reduction in filling pressure after the dialysis procedure may cause reduced cardiac output followed by hypotension (Ekart *et al.*, 2011).

1.8.2(b) Renin angiotensin aldosterone system (RAAS) induced hypertension

Blood pressure is regulated by a signaling pathway called renin-angiotensin-aldosterone system (RAAS). Upon stimulation by hypotension or in certain cases like stressful situations kidneys tends to release an enzyme known as renin, which is responsible for generation of signal transduction pathway. The renin causes protein angiotensinogen to convert into angiotensin-I that is further changed by "angiotensin converting enzyme (ACE into 'angiotensin-II'") (Boulware *et al.*, 2006).

'Angiotensin-II' plays its role in vasoconstriction and simultaneous vasopressin secretion in the pituitary gland. Moreover, it also helps in release of adrenaline, nor-adrenaline and aldosterone. 'Adrenaline and nor-adrenaline' increase 'vasoconstriction' while 'aldosterone' may increase the renal filtration activity. Normal kidneys can usually contain more water & sodium and are capable to excrete higher levels of potassium. The water-retaining hormone *viz.* Vasopressin can prevent the excretion of water without having any significant effect on levels of sodium and potassium. In this process, the total blood volume in the body increases, consequently the constricted arteries would pump more blood that may create higher than normal pressure to be exerted on the artery walls resulting into higher blood pressure **(Fig. 1.1).**

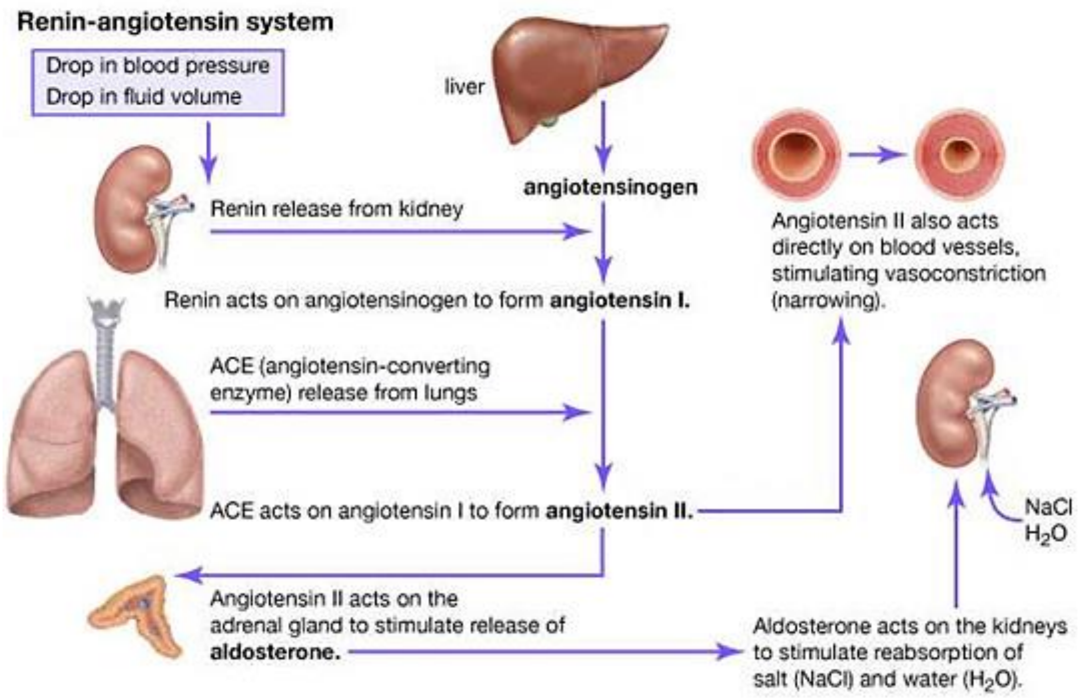

Fig. 1.1 Renin angiotensin aldosterone system pathway (Britannica, 2017)

1.8.2(c) Increased sympathetic activity associated hypertension

Hypertension caused by sympathetic activity is common among ESRD patients. Various studies reported increased sympathetic activity among HD patients (Converse Jr *et al.*, 1992). Moreover, HD patients with bilateral nephrectomy have normal sympathetic activity, which leads towards the sympathetic activity hypothesis which relates to neurogenic signal of the renal afferents arising in the failing kidney (Augustyniak, Tuncel, Zhang, Toto, & Victor, 2002).

It was reported in a study that sympathetic over activity can be normalized by the use of ACE inhibitors and not by calcium channel blockers in patients that are with renin dependent hypertension or with chronic renal insufficiency associated with Angiotensin-II related neural action, asymmetric di-methyl-arginine (ADMA) elevated levels, oxidative stress, nocturnal hypoxia, chronic inflammation and obesity are among the factors that contribute towards increased sympathetic activity (Levin *et al.*, 2010).

1.8.2(d) Parathyroid hormone associated hypertension

Excessive secretion of parathyroid hormone results in inducing of intracellular calcium levels that are believed to be associated with hypertension among ESRD patients. The mechanism accountable for hypertension is based on the fact that vasoconstriction is caused by the calcium available in smooth muscles cells of blood vessels. It is noteworthy that administration of vitamin D or performing parathyroidectomy in patient on dialysis can result in reduction of BP (Raine *et al.*, 1993).

1.8.2(e) Reduced production of prostaglandins/ bradykinins associated hypertension

Normally, kidneys produce various vasodilating chemicals such as prostaglandins, kinins and antihypertensive neural reno medullary lipids. It has been observed that ups and downs in generation of these chemicals usually leads to hypertension in patients on hemodialysis. It has also been found that levels of prostaglandin (PgE2) production are lower in hypertensive HD patients. Moreover, in uremic patients usually a negative correlation exists between BP and prostacyclin metabolite 6-keto-PgF1α (Ekart *et al.*, 2011).

1.8.3 Anemia as a complication of end stage renal disease

Anemia is commonly observed problem with very high prevalence in both early as well as late stages of CKD. Roughly, all of the HD patients suffer from anemia. Anemia is also considered as a risk factor for CV complication, deteriorating life quality that may lead towards cognitive impairment and finally into mortality of the CKD patients (McCullough & Lepor, 2005). The basic mechanism of anemia in ESRD may be summarized as under (Babitt & Lin, 2012):

- Erythropoietin (EPO) decreased production
- Hepcidin, a liver hormone, controls availability of iron and can regulate both absorption of dietary iron as well as recycling of iron from RBCs. In chronic kidney disease, the decreased renal clearance and inflammation leads towards enhanced hepcidin levels that in turn causes the phenomenon of "iron restricted erythropoiesis".
- Erythropoietin related bone marrow's unresponsiveness

1.8.4 Mineral and bone disorder complications

"Systemic disorder of mineral and bone metabolism leads to a clinical syndrome called chronic kidney disease associated mineral and bone disorder (CKD-MBD) which is specifically due to CKD". The following mechanisms have been proposed for CKD-MBD (Komaba & Fukagawa, 2009):

- Abnormal concentrations of parathyroid hormone, phosphate and calcium in serum.
- Disturbances in Vitamin D metabolism.
- Renal Osteodystrophy
- Elevated levels of a hormone viz. fibroblast growth factor (FGF23) which is concerned with the process of metabolism with respect to minerals and Vitamin-D.
- Vascular and soft tissue calcification.

1.8.5 Uremic complication

"Uremic syndrome refers to a series of complications which contribute towards the development and progression of CKD to ESRD". These may include electrolyte disorder, retention of water, hormonal deficiency or resistances, compensatory response to body and last but not the least is retention of waste (Chikotas, Gunderman, & Oman, 2006). These uremic problems are considered to be due to reduction in eGFR and possible damaging action against the excretory and endocrine systems of the body. The common signs and symptoms of uremic complications include loss of appetite, pruritus, elevated level of blood urea and creatinine and neurological changes (Meyer & Hostetter, 2007).

1.8.6 Malnutrition-inflammation complication

It is reported that in early stages of CKD there could arise protein-energy malnutrition which becomes prominent with significant decline in eGFR. The malnutrition-inflammation complex syndrome (MICS) is basically collection of malnutrition and inflammation which generally coexist in CKD (Kalantar-Zadeh, 2005). Inadequate diet results in abnormalities with several clinically markers such as “low albumin and transthyretin, lipids and elevated levels of C-reactive protein (CRP)”. Etiology of protein associated malnutrition in renal impaired patients is not clearly understood. The proposed mechanisms of protein malnutrition in renal impaired patients include resistances to insulin and growth hormone, metabolic acidosis, co-morbid conditions such as infections, aging and cardiovascular disorders (CVD), inadequate dietary intake, oxidative stress and endocrine disorder such as hyperparathyroidism. Lastly, inflammation is believed to be concerned with increased protein catabolism and with pro-inflammatory cytokines release that lead to loss of protein stores (Kalantar-Zadeh, 2005).

1.9 Management of hypertension among hemodialysis patients

In hemodialysis patients, management of hypertension is a complex procedure that requires in depth information about the pharmacokinetic as well as pharmacodynamic properties of the drugs used by such patients. It is considered that modification in life style can enormously affect management of hypertension in HD patients. Moreover, proper strategy of salt restriction is also important rather essentially required. In addition to all these, reduction of extracellular fluid and dry weight achievement are also considered to be among the most important factors in managing hypertension in HD patients and these should never be neglected **(Fig. 1.2)**.

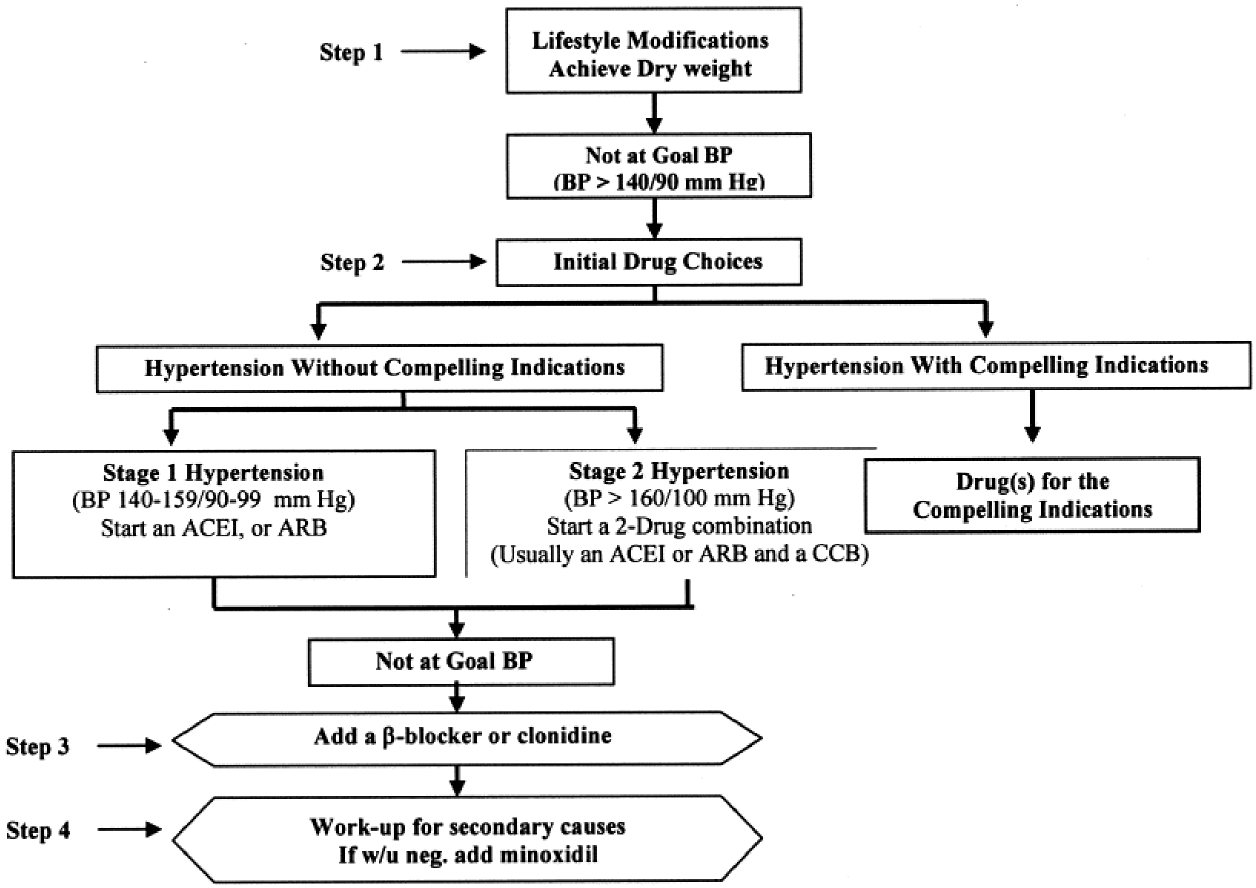

Fig. 1.2 Management of hypertension among hemodialysis patients [*Source: KDOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patient (K/DOQI, 2005)*].

If lifestyle modifications are not that much successful in controlling hypertension, antihypertensive therapy is recommended. NKF KDOQI guidelines recommended that first line antihypertensive agents are ACE inhibitors or ARBs. In HD patients, ARBs can significantly reduce the left ventricular hypertrophy (LVH) and in this connection, they are found to be more effective as compared to ACE inhibitors (Cannella *et al.*, 1997; Guerin *et al.*, 2001; Shibasaki *et al.*, 2002). It has been recommended that in order to achieve control, alpha anti-adrenergic drugs and calcium channel blockers