CHAPTER 2

Literature Rveiew

2.1 Chronic kidney disease

CKD is a disease that increases mortality and morbidity worldwide (1). Incidence is as high as 200 cases per million per year in many countries around the world (1). Similarly, the prevalence of CKD in Thailand is increasing. The prevalence of CKD Stages I, II, III, and IV-V in 2010 were found to be 3.3%, 5.6%, 7.5%, and 1.1%, respectively (16). The prevalence of CKD was not significantly different between males and females, but there is a trend toward prevalence with increasing age (16). Moreover, the prevalence of CKD was higher in Bangkok and the Northern and Northeastern regions compared to the outlying Central and Southern regions (16). However, it is well-recognized that the number of patients with ESRD may reach 2.24 million by 2030 (2, 17). CKD is characterized by kidney damage that shows albuminuria or reduced kidney function with a GFR less than 60 mL/min per 1.73 m^2 for three months or more (18). The causes of CKD may include kidney damage or inflammation due to glomerular and tubulointerstitial diseases, infections and exposure to drugs and toxins, or other factors such as old age, diabetes, hypertension, obesity, cardiovascular disease (CVD), and diabetic mellitus (17). A diagnosis of CKD is classified into five stages on the basis of GFR as follows (19): Stage 1 GFR, more than 90 mL/min per 1.73 m^2; Stage 2 GFR, 60-89 mL/min per 1.73 m^2; Stage 3 GFR, 30-59 mL/min per 1.73 m^2; Stage 4 GFR, 15-29 mL/min per 1.73m^2; and Stage 5 GFR, less than 15 mL/min per

1.73m^2. However, the complications of CKD can occur at any stage, often leading to death with no progression to kidney failure and can arise from the adverse effects of intervention to prevent or treat the disease (1, 17). Stage 5 of CKD, a GFR less than 15 mL/min per 1.73 m^2, is called ESRD (19). In this stage, patients need to be treated with renal replacement therapy (RRT), which is dialysis or transplantation. Dialysis treatments include hemodialysis and peritoneal dialysis techniques.

2.1.1 Complications of CKD

CKD patients have complications from the disease. Common complications are listed below.

2.1.1.1 Cardiovascular system complications consist of hypertension, anemia, diabetics, heigh serum triglycerides (TG) levels, and low levels of high density lipoprotein (HDL) cholesterol. Hypertension presents a unique CVD issue in the ESRD patients (18). Hypertension is increasing in CKD patients, as are the other cardiac disorders, which are associated with poorer dialysis outcomes (18). Hypertension occurs in approximately 80% of ESRD patients. The prevalence of hypertension in dialysis patients has increased, with over 50–60% of hemodialysis patients and 40–90% of continuous ambulatory peritoneal dialysis (CAPD) patients (18). Hypertension is attributed to salt retention and an increase of vascular tone due to a failure to suppress the sympathetic nervous system and renin-angiotensin system, inhibition of sodium-potassium adenosine triphosphate (ATPase), and nitric-oxide deficiency (1). Expanded extracellular fluid volume from fluid overload associated with sodium retention is the most prevalent cause (20). There is also an increased risk of cardiovascular morbidity in

this patient group (20). Anemia is the most common and severe hematologic defect in CKD patients. The causes of anemia in ESRD patients include the failure to produce or an inhibition of the action of erythropoietin, a hormone produced by the kidney that stimulates the bone marrow to produce red blood cells, a shortened life span of the red blood cells, impaired intake of iron, blood loss caused by platelet abnormalities, blood loss related to a dialysis procedure, elevated levels of parathyroid hormone (PTH), which has a suppressive effect on erythropoiesis in the bone marrow, and poor nutrition and diet (20). The effects of anemia are fatigue, pallor, shortness of breath, and poor exercise tolerance (20). The treatment of anemia with exogenous erythrocyte stimulating agents (ESA) raises hemoglobin, which reduces the need for transfusions, and improves quality of life and exercise capacity (1). However, treatment with ESA for target hemoglobin concentrations of 130 g/L or more (achieved mean concentrations > 110 g/L or 120 g/L) has been consistently associated with high rates of CVD, especially in patients who are ESA hyporesponsive (1). Diabetics represent about 35% of all dialysis patients (21). Furthermore, non-diabetic CKD patients often have glucose intolerance, may be due to peripheral insulin resistance (21). Insulin resistance is primarily detectable when GFR is less than 50 mL/min. Reduced insulin-mediated non-oxidative glucose displacement is the most evident defect of glucose metabolism, but impairments of glucose oxidation, the defective suppression of endogenous glucose production, and abnormal insulin secretion also contribute to uremic glucose intolerance (22). It has been reported that insulin resistance may be related to arterial hypertension (23) and high cardiovascular morbidity and mortality in CKD patients (24, 25). The underlying mechanism can be an impaired synthesis of nitric oxide (NO) in the

endothelium of CKD patients. It was reported that functioning endothelial NO synthase (eNOS) is important for the control not only of arterial pressure but also of glucose and lipid homeostasis (26). Serum triglycerides (TG) are elevated in CKD patients because of increased production of TG-rich lipoproteins such as very-low-density lipoproteins (VLDL) in the liver (27) and dysfunction of TG degradation resulting from insufficient mitochondrial beta-oxidation of fatty acids. This can be caused by a deficit of L-carnitine, especially in hemodialysis patients (28, 29). Hyperinsulinemia is the main factor increasing synthesis of TG and decreasing the activity of lipoprotein lipase. The most important changes in lipid metabolism found in many CKD patients are high serum TG levels and low of high-density lipoprotein (HDL) cholesterol levels (30). It is well known that HDL cholesterol levels are inversely correlated with the risk of atherosclerosis (31).

2.1.1.2 Musculoskeletal system complications include mineral and bone disorders, muscle weakness, skeletal myopathy, malnutrition, and inflammation. Minerals and bone disorders are characterized by abnormalities in serum concentrations of calcium, phosphorus, 1, 25-dihydroxycholecalciferol, and parathyroid hormone. Abnormalities in bone morphology such as osteomalacia, osteitis fibrosa, osteoporosis, osteosclerosis, growth retardation (in children), metastatic calcification, and osteodystrophy were found in CKD patients (18). Phosphate retention and deficiency of 1, 25-dihydroxycholecalciferol are causes of hyperparathyroidism and hypocalcaemia (1). Fibroblast growth factor (FGF)-23, a bone-derived phosphaturic hormone, is secreted in response to phosphorus intake and inhibits production of 1, 25-dihydroxycholecalciferol, which is associated with CVDs (1). Many ESRD patients

complain of muscle weakness and easy tiring supported by skeletal myopathy (32). ESRD patients showed atrophy of the type II muscle fibers (33, 34), marked variability of fiber area (34, 35), lower proportion of type IIB muscle fibers (36), fiber splitting (35, 37), and degenerative changes including abnormalities of multiple mitochondrial (33, 37). After ESRD patients received recombinant human erythropoietin (rHu-EPO) treatment, there was an improvement of the histological appearance of skeletal muscle. In particular, distribution of type I muscle fibers returned to normal and improved the diameters of type IIA and IIB muscle fibers (35). Malnutrition and inflammation frequently coexist in CKD patients (1). Decreased energy intake is an important causal factor, but dietary interventions are usually not sufficient to increase intake (1). Inflammation might be partly a result of underlying systemic vascular disease and a way to retain solutes (1). Infection is the second most common cause of death in ESRD patients (25).

2.1.1.3 Metabolic system complications include acid-base disorder and uremic manifestations. Acid-base disorder is common in CKD patients. Metabolic acidosis is prevalent in a majority of CKD patients and occurs when GFR is less than 20 to 25% of normal levels. The degree of acidosis approximately correlates with the severity of CKD and is severe at a lower GFR. Metabolic acidosis can be the high-anion-gap type, although the anion gap can be normal or only moderately increased even with stage 4 or 5 CKD (38). In mild chronic renal insufficiency, metabolic acidosis is the result of reduced reabsorbed bicarbonate, excreted ammonia, and eliminated titratable acid excretion. In more severe renal insufficiency, organic and other conjugate anions of acids cannot be sufficiently excreted, and elevated anion gap acidosis appears (39).

Uremic manifestations are the result of accumulated toxins and disrupted excretory and hormonal functions (40). The symptoms from uremia are fatigue, weakness, frailty, and decreased health-related quality of life (1).

2.1.1.4 Neurological system, both the central nervous system (CNS) and the peripheral nervous system (PNS) are affected by CKD (41). Retained toxins are thought to have a role in these disorders, and intensive dialysis has been linked with amelioration (42). Peripheral neuropathy was found to cause patients to have weakness and disability (41). The signs of PNS and CNS disorders include peripheral neuropathy, restless leg syndrome, sleep disorders, and cognitive impairment. However, these signs can improve after renal transplantation (41).

2.1.2 Management of CKD

Disease management is based on clinical diagnosis and stage according to GFR and albuminuria level (1). The disease stage can be used to guide non-specific therapies to slow progression and reduce the risk of complications (1, 17). Renal replacement therapy (RRT) is a treatment for CKD patients in ESRD. Renal replacement treatment consists of dialysis and transplantation treatments (1, 17). Kidney transplantation has become the preferred treatment of ESRD. Kidney transplantation procedures can be divided into several types based on the relationship between the recipient and the donor. These include decreased donor renal transplants (17). The advantages of kidney transplantation are improved quality of life, reduction in the risk of dying, and improved survival, (42) and the disadvantage of kidney transplantation is the recipient's required lifelong treatment with immunosuppressive drugs, which has associated risks of

infection and malignancy in transplantation patients (17). Dialysis treatment includes peritoneal dialysis (PD) and hemodialysis. This process removes waste products, such as uremia toxins, excess extracellular fluid, and electrolytes (sodium and potassium), by equilibrating the patient in terms of blood to dialysate fluid through a semi-permeable membrane (17). The advantages of dialysis treatment are decreased morbidity and mortality, improve quality of life, improved rehabilitation, and decreased hospitalization expenses (18). However, there are the disadvantages of dialysis treatment, such as hypotension, cramps, dialyzer reactions, hypoxemia, febrile reactions, dialysis disequilibrium syndrome, bleeding, pruritus, heart rate disturbances and arrhythmias, cardiopulmonary arrest during dialysis, and air embolism (18). Peritoneal dialysis uses the peritoneum of patients as the semi-permeable membrane. Dialysis is inserted into the peritoneal cavity to pass a catheter and is left to equilibrate with the blood before it is drained out and replaced with fresh fluid. The osmolality of the dialysate can be changed by the concentration in the glucose. It can control the quantity of extra fluid for drainage (17). The advantages of peritoneal dialysis are its portability and low cost. It is easy to learn but requires several weeks of training before initiation. In addition, PD allows for more gradual fluid removal and somewhat unpredictably tends to permit greater hemodynamic stability for patients with severe cardiomyopathy (42). However, the disadvantage of peritoneal dialysis is a risk of infection such as peritonitis as a result of the contamination of the fluid during the exchange procedure, usually by a Staphylococcus species (17). Hemodialysis involves the removal of toxins and waste products with dialysis. Solutes are removed largely by diffusion down a chemical gradient, and ultrafiltration results from the hydrostatic pressure gradient. Hemodialysis

was first used in the 1940s for the treatment of acute renal failure. It is now the most common form of renal replacement for ESRD patients in the United States (18). Hemodialysis is a highly successful life-saving and life-sustaining therapy. With its complementary treatments, peritoneal dialysis, and renal transplantation, it has revolutionized the outlook for patients with ESRD (43). Approximately 91.9% of patients diagnosed with ESRD receive maintenance hemodialysis (44). Hemodialysis treatment requires around 4 hours to complete and must be performed several times per week according to the severity of the kidney disease (45). The dialysis machine draws up and warms purified water to physiological temperatures. The heated water then undergoes desecration under a vacuum to prevent dissolved air from escaping the solution as negative pressure is applied during dialysis (46). The heated and desecrated product water is then mixed with the concentrate to produce dialysate. To ensure proper proportioning, the conductivity monitor downstream from the proportioning pump continuously measures the electrical conductivity of the product solution. Because malproportioned dialysate may cause severe electrolyte disturbances in the patient leading to death, the conductivity monitor has a narrow range of tolerance and is usually redundant (46). The dialysate circuit must be able to generate both negative and positive dialysate pressures within the dialyzer because many dialyzers require a negative dialysate pressure for filtration dialyzer with high ultrafiltration coefficient (Ku_f), or conditions that increase pressure in the blood compartment require a positive dialysate pressure to limit filtration (46).

The basis of hemodialysis is the movement of solutes and water across semi-permeable membranes by diffusion and convection. Diffusion is the movement of solutes across a

semi-permeable membrane down a concentration gradient. The diffusive clearance of a solute depends on its molecular weight, electrical charge, blood dialysis fluid concentration gradient, blood and dialysis flow rates, and the membrane's characteristics (diffusion coefficient). Smaller molecules such as urea are cleared well, whereas larger molecules such as albumin cannot pass through the membrane. The clearance of mid-sized molecules such as b2-microglobulin can be improved by using high-flux membranes, which have pores of sufficient size to allow the passage of such molecules. Convection refers to the movement of solvents and dissolved solutes across a semi-permeable membrane, down a hydrostatic pressure gradient. Convection improves a mid-sized molecule's clearance. Ultrafiltration is the convective movement of water across a membrane. The ultrafiltration rate depends on the hydrostatic pressure difference across the membrane and on its permeability to water (ultrafiltration coefficient) (43). The dialyzers consist of semi-permeable membranes arranged to form separate adjacent paths for blood and dialysis fluid, which flow on opposite sides of the membrane in opposite directions to maximize diffusion gradients. Dialyzers are classified by their designed geometry, membrane composition, surface area, permeability characteristics (diffusion and ultrafiltration coefficient), and biocompatibility characteristics. Currently, hollow fiber dialyzers are the most commonly used type (43). During dialysis, solutes must diffuse from body tissues into the blood to reach the dialyzer. Even within the dialyzer, as blood passes through it, solutes must diffuse from within red cells to the plasma before diffusion can take place across the dialyzer membrane into the dialysate. Even for urea, which diffuses easily across cell membranes from tissue to blood, some disequilibrium still develops among

the various body compartments during dialysis, as reflected in the postdialysis. As a result, the patient's clearance, defined as the urea removal rate divided by the average urea concentration in total body water, is always less than the dialyzer clearance. Whole body clearance is a virtual clearance that can be derived from single compartment modeling of the predialysis and equilibrated postdialysis BUN (46). Adding further complexity to the concept of clearance are the frequency and duration of dialysis. Because residual native kidney clearance (Kr) exerts most of its effect between dialyses, when dialyzer clearance is zero, it cannot be directly added to dialyzer clearance (46). The patient's interdialytic weight gain reflects fluid retention between two consecutive hemodialysis treatments, which will then be removed rather quickly via dialysis ultrafiltration (UF) during a 4-hour dialysis treatment (14). The effects of isolated ultrafiltration are comprised of the hemodynamic effect, acid-base effect, and hematologic effect. First, for the hemodynamic effect, isolated ultrafiltration is better tolerated in terms of circulatory stability than is fluid removal during conventional hemodialysis. The rapid drop in plasma osmolality occurring in conventional dialysis but not in isolated ultrafiltration promotes hypotension. Fluid removal by isolated ultrafiltration during hemodialysis was found to decrease cardiac output, stroke volume, and pulmonary capillary wedge pressure and plasma volume. Conventional hemodialysis was found to decrease blood pressure, increase heart rate, and increase total peripheral resistance (18). Second, for the acid-base effect, blood pH did not change during isolated ultrafiltration, but it has been show that a mild drop in the plasma bicarbonate concentration occurs after removing 1–3 L of ultrafiltration over 1–2 hours (18). Third, for the hematologic effect, a slight hemoconcentration occurred as a

result of removing fluid from the blood space with an increase in hematocrit, plasma proteins, and plasma oncotic pressure (18).

Although dialysis therapy is life-sustaining, patients still have complications from dialysis treatment, including disequilibrium syndrome, cardiac arrhythmias, hypotension, cramping, problems with bleeding, and fatigue (43, 47). Studies have shown that the ability to perform physical exercise in ESRD patients who are treated with dialysis was reduced by 30–40% when compared with healthy individuals of the same age (45, 48). Moreover, patients who had dialysis treatment were found to have a aerobic peak power or VO_2 peak of only half of that expected for normal subjects of the same age (49-52). In addition, patients with ESRD have very low self-reported levels of physical functioning and low scores in quality of life measured with the SF-36 questionnaire (36, 53). The advantages of hemodialysis are that it is relatively straightforward and simple to initiate. It can adequately substitute normal renal function for extended periods of time, although it has the disadvantage of being associated with a certain amount of expense and complexity. In addition, hemodialysis requires adequate staffing and supervision; this has been a tremendous hurdle for many centers, given the shortage of qualified personnel (42).

In conclusion, CKD patients have complications in many systems, including the cardiovascular, musculoskeletal, and neurological systems. The main cause of these complications was from uremia. According to the severity of CKD, patients have to endure the deterioration of physical status and health. Although dialysis therapy is a life-sustaining treatment, patients still have complications from it. Deterioration of physical health causes a loss of mobility, resulting in higher rates of hospitalization,

morbidity, and mortality in CKD patients. Therefore, an evaluation of the physical performance of CKD patients who experience complications from uremia could be used as primitive data for planning therapeutic treatment and could be help to promote physical well-being in this group of patients.

2.1.3 Pharmacological therapy of CKD

Hemodialysis patients have to use medication for treatment, including blockers of the renin-angiotensin-aldosterone system (RAAS): RAAS are generally avoided by most physicians in the patients who would garner the greatest benefit, specifically those with an eGFR less than 50 ml/min/1.73m^2 with proteinuria, angiotensin-converting enzyme inhibitors (ACE): ACE inhibitor blunt the rise in GFR that follows a protein load by blocking this afferent arterial dilation , angiotensin II receptor blockers (ARB): ARB is associated with a lower incidence of cough, angioedema, taste disturbances and hyperkalemia, direct renin inhibitors: the role for aliskiren in the management of hypertension has yet to be fully determined but it effectively reduces BP, aldosterone antagonists: aldosterone antagonists use for treating hypertension in patients with advanced heart failure and following myocardial infarction, diuretics, calcium channel blockers (CCB): CCB should be used aggressively for BP reduction in patients without proteinuric kidney disease, β-adrenergic blockers, aspirin: β-adrenergic antagonists use for treating hypertension, and vitamin D: Vitamin D has direct effects on podocyte proliferation and differentiation that appear to prevent apoptosis, cell death and improve the metabolic milieu of the kidney (46).

2.2 Energy

The energy requirement of an individual has been defined by a recent international working group such as the level of energy intake from food that will balance energy expenditure when the individual has body size, body composition, and a level of physical activity consistent with long-term good health and that will allow for the maintenance of economically necessary and socially desirable physical activity (54).

2.2.1 Estimating energy requirements

Total energy expenditure (TEE) comprises the energy expended at rest, physical activity, and as a result of thermogenesis. On the other hand, these are affected by several variables, including age, sex, body size and composition, genetic factors, energy intake, physiologic state, coexisting pathological conditions, and ambient temperature (54). In addition, energy requirements decrease as adults age (55, 56) because of a decline in physical activity (57) and a decline in metabolic rate associated with losses of fat free mass (FFM) (58). For many elderly individuals, decreased energy expenditure may not be matched by decreased energy intake, thereby contributing to an increase in body fat and the onset of obesity. In elderly adults who maintain energy balance, the reduced energy and nutrient intakes may contribute to the development of nutritional deficiency states. This risk may be especially high in the oldest and most frail elderly people (59). The previous study found that TEE was related to VO_2max, and this relationship was independent of differences in FFM (60). This finding can be interpreted in two ways:1) the increased TEE is associated with a physically active life-style and leads to a higher VO_2max; 2) the individuals with a higher VO_2max as a result

of genetic factors and regular participation in physical activity engage in physical activities more frequently because of their higher work capacity (60). In addition, several studies suggest that obese individuals have decreased energy expenditure, which might predispose them to gain weight or regain lost weight (57, 61, 62). Moreover, the previous study data confirms these findings and indicates that the metabolic rate decreases with weight reduction in conjunction with decreases in lean body mass, and that TEE decreases in conjunction with decreases in total weight (63). Energy expenditure was adjusted for differences in body composition, age, and activity (64). In addition, this study found that energy expenditure was higher in males than in females (64).

2.2.2 Resting energy expenditure

REE is the largest component of total energy expenditure. REE represents the energy expended by a person at rest under conditions of thermal neutrality. Basal metabolic rate (BMR) is more precisely defined as the REE measured soon after awakening in the morning at least 12 hours after the last meal. REE is not usually measured under basal conditions. REE may include the residual thermal effect of a previous meal and may be lower than BMR during quiet sleep. In practice, BMR and REE may differ less than 10%, and the terms are used interchangeably (54). In patients with diseases involving organs that have important metabolic functions, energy metabolism is frequently altered (65-67). For example, the kidneys have important metabolic functions and perform a number of oxygen-dependent activities (68). Oxygen consumption by the kidneys rises as a function of GFR (68). Moreover, a previous study suggested that renal failure is associated with a hypometabolic and hypothermic state due to profound abnormalities

in cell metabolism (69). Actually, the study of Kurnik et al. (69) showed that patients with moderate loss of renal function have lower renal blood flow and lower renal oxygen consumption than healthy individuals. Therefore, it is possible that CKD patients who have decreasing GFR may have reduced REE (69). Furthermore, the previous study found that inflammation was associated with increased REE in CKD patients (3). However, the mechanisms involved in high REE cannot be fully identified (3), but the metabolic disorders of the inflammatory response include fever (4), elevated VO_2 (4), enhanced lipolysis and fat utilization (5), elevated concentration of catabolic hormones, extensive protein catabolism (6), and elevation in REE. In addition, the maintenance of immune function was estimated to account for as much as 15% of daily energy expenditure (40). The importance of these findings is related to the deleterious effects of a sustained elevated REE. Moreover, its negative effects on nutritional status and increased REE have been associated with a high rate of mortality in patients who receive dialysis (3). Previous studies (7, 8) have found that energy expenditure increases in association with hemodialysis procedure may be due to the negative nitrogen balance that could result from amino acid loss in dialysate and from increased protein catabolism. In additional, the dialysis procedure may remove the fuel substrates such as amino acids, peptides, glucose metabolites (i.e., pyruvate and lactate) (7, 8). All of the foregoing factors might be expected to increase energy expenditure and the dietary requirement for energy sources (9). Monteon et al. (9) studied the energy expenditure of hemodialysis patients and compared the energy expenditure of hemodialysis with healthy controls. The result showed that REE adjusted for body surface area of CKD patients was not different from that of healthy subjects. Moreover, no difference was

found in energy expenditure while patients were sitting, during physical activity, and after food intake (9). However, a study showed the differences in REE comparing CKD patients with healthy subjects. The study of Ikizler et al. (10) found that the REE of hemodialysis patients were significantly higher on nondialysis days when compared with age- and gender-matched healthy controls (10). The calculation of REE is based on the observation that the oxidation of quantity of carbohydrate, fat and protein each generates an amount of energy and carbondioxide and consumes a quantity of oxygen that is characteristic and predictable (70). The ratio of the oxygen consumed to the carbon dioxide produced indicates the relative oxidation of fat versus carbohydrate and protein. The urea nitrogen appearance enables one to estimate the quantity of protein that is oxidized (71). From these relationships, it is possible to estimate REE according to the following the Weir equation, (72) without using urinary urea nitrogen level. Basal metabolic rate (BMR) (kcal / min) = 3.9 [VO_2 (L / min) + 1.1 [VCO_2 (L / min)], where VO_2 is volume of oxygen and VCO_2 is volume of carbon dioxide. After BMR values were calculated for the REE, which is equal to the REE: REE (kcal / d) = BMR x 1, 440 min. The intraindividual variation coefficient for REE obtained from 9 healthy subjects studied on 2 occasions was 5% (72).

2.2.3 Physical activity

The second largest component of TEE is physical activity. Previously, estimates of energy requirements were based in part on the different physical activity levels associated with different occupations. With the introduction of labor-saving machinery, occupational energy expenditures and differences between occupations tended to decline (10). Physical activity substantially improves health and function in the general

population. Higher levels of physical activity are associated with lower mortality in a dose-dependent manner (73, 74). Underlying this survival benefit is the reduced impact of many major diseases in physically active individuals. Patients on dialysis have very low levels of physical activity when compared with sedentary individuals (75). Moreover, patients on dialysis carry an immense burden of physical disability and chronic disease. Sedentary patients starting dialysis have 60% higher one-year mortality than their physically active counterparts (76). Muscle atrophy has been identified as a potential contributing cause for low levels of physical activity in patients on dialysis (77-79). Muscle atrophy is further linked with both malnutrition and inflammation (79).

2.2.4 Metabolic response to food

Metabolic rate increases after eating reflect the size and composition of the meal. It reaches a maximum approximately 1 hour after the meal is consumed and virtually disappears 4 hours afterward. In relation to total energy expenditure, the thermic effect of meals is relatively small, on the order of 5 to 10% of the energy ingested. Small differences in this component of energy expenditure could have significant cumulative long-term effects but are generally undetectable, being lost in the day-to-day variation in energy metabolism (10). Currently, energy expenditure in hemodialysis patients has recently shown an increase in energy expenditure during hemodialysis treatment. As of now, the comparison of energy expenditure between pre- and post- hemodialysis treatment in hemodialysis patients has not been studied. Therefore, the purpose of this study is to evaluate energy expenditure among pre-, during, and post- hemodialysis treatment in hemodialysis patients. The energy expenditure measurement that will be employed in this study is indirect calorimetry using a PhysioFlow® (Manatec, France).

2.3 Hemodynamics

Interindividual differences in central and peripheral hemodynamics have become increasingly important to the understanding of arterial pressure regulation (80, 81). In young healthy men, total peripheral resistance (TPR) is positively related to muscle sympathetic nerve activity (MSNA), suggesting that MSNA is a good index of net whole-body vasoconstrictor tone. However, the men with higher levels of MSNA and TPR do not necessarily have higher resting arterial pressure (82). Previous studies found that young men with high MSNA had a lower cardiac output and less α-adrenergic receptor vasoconstrictor responsiveness, reducing the net effect of high MSNA on arterial pressure (82). In young women, blood pressure is typically lower than that observed in men of the same age (83, 84). Furthermore, the incidence of orthostatic hypotension is greater in women than in men (85), and women have lower tonic autonomic support of baseline arterial pressure (86). Women also exhibit blunted vasoconstrictor responses to α-adrenergic stimulation, (87) which may be related to the vasodilator effect of estrogen (88, 89). Several mechanisms may contribute to the lack of a relationship between sympathetic nerve activity and TPR in women. First, estrogen has a direct vasodilator effect on the vasculature, which might compete with sympathetic vasoconstriction (88, 89). Second, estrogen appears to increase the bioavailability of NO, which again might offset sympathetic vasoconstriction (90). Third, estrogen supplementation in rats was found to increase vasodilating β2-adrenergic receptor-mediated responses to isoproterenol (91). Age-related increases in systolic blood pressure (92, 93) or of heart rate at rest (94) would be expected to increase myocardial oxygen demand and consequently blood flow. Accordingly, the

observed myocardial blood flow reserve might be attenuated in older subjects (95). Lewis et al. (96) found that a small decrease in cardiac index in 100 male subjects between 40 and 89 years of age. They considered that the observed changes represented neither statistically nor physiologically a significant decline and those were predominantly the result of a decrease in oxygen consumption (96).

Hemodynamic risk factors in CKD relate to volume and pressure overload of the cardiovascular system. They form a substantial part of the overall cardiovascular risk that kidney disease patients face. There is now ample evidence that these risk factors exert their effects from an early stage of kidney disease and that, subsequently, patients are subject to a complex but synergistic interplay of destructive vascular events as their renal function declines. As a consequence, premature mortality from CVD is extremely high (97-99). Although recognized as the most common cause of volume overload, the actual circulating blood volume in anemic CKD patients is not increased. The deleterious effects of anemia are related to sustained hemodynamic efforts to maintain sufficient oxygen supply to enable normal tissue metabolism (100-102). The measurement of hemodynamic parameters will include stroke volume, heart rate, cardiac output, end-diastolic volume, ejection fraction and total peripheral resistance.

2.3.1 Anemia

The most common cause of volume overload in the actual circulating blood volume in anemic CKD patients is not increased (103-105). The deleterious effects of anemia relate to sustained hemodynamic efforts to maintain sufficient oxygen supply to enable normal tissue metabolism. This becomes increasingly manifest as the hemoglobin (Hb)

concentration falls below 120g/L with an increase in cardiac output and peripheral oxygen extraction and a decrease in peripheral resistance (2,6).

2.3.2 Increased extracellular volume

Increase extracellular volume (ECV) is predominantly seen in dialysis patients in whom it is common and an independent risk factor for cardiovascular morbidity and mortality (106). Patient reactions during hemodialysis still remain a significant problem in any chronic dialysis program, including hypotension, hypertension, pulmonary edema, and headaches. The dialysis program might well be related to changes in the cardiovascular system during hemodialysis (15). In addition to a tendency to retain fluid, patients undergoing long-term dialysis have other similarities to heart failure patients; they both have excessively high mortality (currently 20% to 25% per year in the United States). Hence, studying the risk factors of poor survival in the dialysis patient population may help advance strategies to mitigate high mortality in dialysis patients, because fluid retention is a major morbid condition in this population. Fluid retention is the main clinical feature in several pathological conditions, including a number of renal and cardiovascular disorders. Fluid overload is usually the main manifestation of decompensate heart and kidney failure, so that not infrequently, these two conditions cannot be distinguished from each other solely on the basis of clinical signs or symptoms (107). In advanced heart failure, compensatory mechanisms may lead to maladaptive consequences (108). Increased activity in the sympathetic nervous system, rennin angiotensin aldosterone system, and increased antidiuretic hormone release can lead to a vicious circle in that augmentation of preload, contractility, and afterload via these mechanisms may worsen fluid overload (109-111). Moreover, hemodialysis

patients cannot maintain an edema-free state, or their target weight despite frequent use of hypertonic exchanges and dietary restriction will cause ultrafiltration failure (UFF). The observed increase in solute transport with time on dialysis explains, in part, the more frequent occurrence of signs and symptoms of UFF rather than that of inadequate solute removal (43). When patients have signs or symptoms of fluid overload, it is important to obtain a good medical history and to perform a through physical examination. Issues such as compliance with diet and dialysis are obviously critical, and a significant reduction in urine output may identify another potential reason for this problem (43).