CHAPTER II

LITERATURE REVIEW

1. The Urinary System

The urinary system is composed of pairs of the kidneys and ureters, the urinary bladder, and the urethra (Figure 1). The system rids the body of waste materials and controls the volume and composition of body fluid. This process depends on highly specialized cells in the kidneys. The kidneys are the two bean-shaped organs, lying against the dorsal body wall in the upper abdomen. The urinary system has three major functions, which are *(51, 52)*

(1) Excretion, or the removal of organic waste products from body fluid;
(2) Elimination, or the discharge of these waste products into the environment;
(3) Homeostatic regulation of the volume and solute concentration of blood plasma.

The excretory functions of the urinary system are performed by these two kidneys. A major function of these kidneys is to remove waste products and excess fluid from the body. These waste products and excess fluid are removed through the urine. The production of urine involves highly complex steps of excretion and reabsorption. This process is necessary to maintain a stable balance of body chemicals. That is why the kidney is one of the major homeostatic devices of the body. In addition to removing waste products generated by cells throughout the body, the urinary system has several other essential functions including:*(51-53)*

(1) Regulating blood volume and blood pressure, by adjusting the volume of water lost in urine, releasing erythropoietin, which stimulated red blood cell production, and releasing rennin, which helps regulate blood pressure and kidney function;
(2) Regulating plasma concentration of sodium, potassium, chloride, and other ions, by controlling the quantities lost in urine and controlling calcium ion levels through the synthesis of calcitriol;
(3) Helping to stabilize blood pH, by preventing their excretion in urine while excreting organic waste products—especially nitrogenous wastes, such as urea and uric acid.

2. Renal Failure

Renal failure occurs when the kidneys are unable to perform the excretory functions, which is needed to maintain homeostasis. When kidney filtration slows for any reasons, urine production declines. As the decline continues, symptoms of renal failure appear because water, ions, and metabolic wastes are retained *(51)*. Virtually all systems in the body are affected; for example, fluid balance, pH, muscular contracting, metabolism, and digestive function are disturbed. The individual generally becomes hypertensive while anemia develops due to a decline in erythropoietin production. Moreover, central nervous system (CNS) problems can lead to sleeplessness, seizures, delirium, and even coma. Renal failure can be classified as acute or chronic.

2.1 Acute renal failure (ARF) is an abrupt reduction in kidney function that is characterized by oliguria, defined as a urine output of 400 milliliters/24 hour (h) or less *(54)* and a sharp rise in nitrogenous compounds in the blood. The concentration of nitrogenous wastes in blood is often assessed by the blood urea nitrogen (BUN) test. It is pointed out that a high BUN result indicates failure of the kidneys to remove urea from the blood *(52)*. Acute renal failure can be caused by various factors; for instance, exposure to nephrotoxic drugs, renal ischemia, urinary obstraction, or trauma that alter blood pressure or otherwise affect glomerular filtration. These cause filtration to slow suddenly or to stop. The reduction in kidney function occurs over a period of a few days and persists for weeks. Besides, sensitized individuals can develop ARF after an allergic response to antibiotics or anesthetics *(51)*. However, if the underlying cause of renal failure is attended to, recovery is usually rapid and complete.

2.2 Chronic renal failure (CRF) is slow, progressive condition resulting from the gradual loss of nephrons. There are numerous diseases that may result in the deterioration of kidney function, including infection, diabetes mellitus, glomerulo-nephritis, tumors, systemic autoimmune disorders, and obstructive disorder *(51-53)*. As kidney function is lost, the glomerular filtration rate (GFR) decreases, causing higher BUN levels. The condition generally cannot be reversed; its progression can only be slowed.

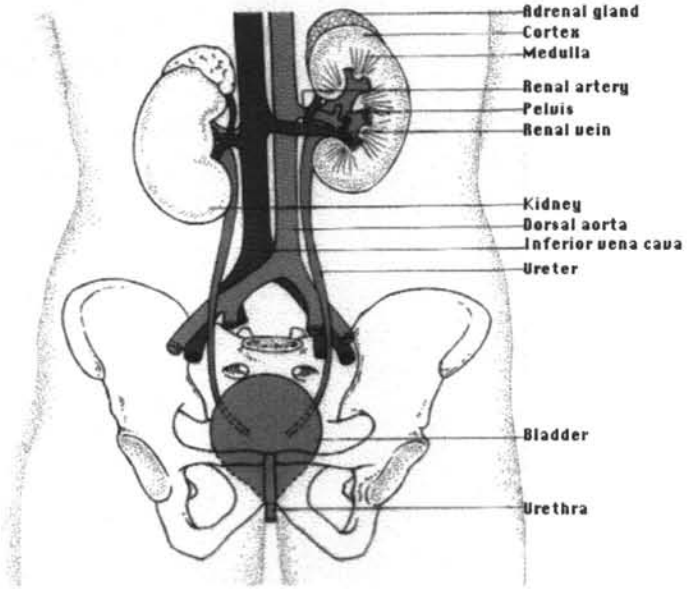

Figure 1 The depict of the urinary system

3. Chronic Kidney Disease

CKD is defined as either kidney damage or glomerular filtration rate less than 60 ml/min for three months or more *(55)*. This is invariably a progressive process that results in end-stage renal disease (ESRD). It is a pathophysiologic process with multiple etiologies, which results in the failure of nephron number and function *(56)*. As renal function deteriorates towards ESRD, a number of physiologic alterations occur, many of which are detrimental. Thus, ESRD represents a clinical state or condition in which there has been an irreversible loss of endogenous renal function, of a degree sufficient to render the patient permanently dependent upon renal replacement therapy in order to avoid life-threatening uremia *(56, 57)*.

The Nephrology Society of Thailand provides statistics on individuals with ESRD, which includes individuals with kidney failure who are receiving dialysis. The overall incidence of ESRD reported in 2004 was 124 cases per million population (pMp) and prevalence of ESRD was 236 cases pMp *(58)*. This registry also stated the incidence of ESRD patients with dialysis 120.78 cases pMp, including incidence of hemodialysis and continuous ambulatory peritoneal dialysis (CAPD) patients, which were 115.38 and 5.4 cases pMp respectively *(58)*. In addition, the prevalence of total patients with dialysis was 211.95 cases per million population representing the prevalence of hemodialysis and CAPD patients that were 200.22 and 11.73 cases per million population *(58)*.

3.1 Classification

Chronic renal disease is divided into five stages on the basis of renal function to denote the severity of renal impairment (Table 1). Glomerular filtration rate is the standard for determining kidney function, but its measurement remains cumbersome. For practical purposes, calculated creatinine clearance is used as a correlate of glomerular filtration rate and is commonly estimated by using the 'Cockcroft-Gault formula'

$$\text{Creatinine clearance} = \frac{(140 - \text{age})(\text{weight in kilograms})}{\text{Serum creatinine (mg/dl)} \times 72} \times (0.85 \text{ if female})$$

Equation 1 Cockcroft-Gault formula

or the recently described modification of diet in renal disease equation (MDRD).

$$\text{Glomerular filtration rate} = 186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female})$$

Equation 2 Modification of diet in renal disease equation

Table 1 Stages of renal dysfunction (adapted from National Kidney Foundation—K/DOQI) *(59)*

Stage	Description	Creatinine clearance (mL/min/1.73 m^2)
1	Normal or increased GFR	>90
2	Early renal insufficiency	60-89
3	Moderate renal failure	30-59
4	Severe renal failure (pre-end stage renal disease)	15-29
5	End stage renal disease (uremia)	<15

GFR = glomerular filtration rate

3.2 Uremic syndrome

The term uremia was first coined in 1847 to indicate a condition caused by contaminating the blood with urine *(60)*. It is a complex state with a constellation of distinctive signs and symptoms that result from renal failure. However, not all patients with renal failure are uremic, but the presence of uremic symptoms typically indicated the need for dialysis therapy. The long-term survival of dialysis patients attests to the importance of low to middle molecular weight factors in causing uremia *(60)*. The manifestations of the uremic syndrome are listed in Table 2.

4. Treatment of Renal Failure

The management of chronic renal failure typically involves restricting water and salt intake and minimizing protein intake, with few dietary proteins allowed *(51)*. This combination reduces strain on the urinary system by minimizing the volume of urine produced and preventing the generation of large quantities of nitrogenous wastes. However, if drug and dietary controls cannot stabilize the composition of blood, more drastic measures are taken. End-stage renal disease can be treated by extracorporal blood purification, peritoneal dialysis, or transplantation. The different therapies are not competing. The selection appears to be more relative to nonmedical factors such as finance, reimbursement, physician preference, and social mores *(61)*. The basic principle involved in this process, called dialysis, is passive diffusion across a selectively permeable membrane. The patient's blood flows past artificial dialysis membrane, which contains pores large enough to permit the diffusion of small ions, but small enough to prevent the loss of plasma protein. On the other side of the membrane flows a special dialysis fluid *(51, 54)*. Dialysis solution typically contains sodium, potassium, calcium, magnesium, chloride, and bicarbonate or acetate. The potassium concentration is somewhat lower than in plasma, resulting in removal of potassium and phosphate from the bloodstream and the addition of bicarbonate *(54)*. The composition of typical dialysis fluid is indicated in Table 3.

As diffusion takes place across the membrane, the composition of the blood changes. Potassium ions, phosphate ions, sulfate ions, urea, creatinine, and uric acid diffuse across the membrane into the dialysis fluid. Bicarbonate ions and glucose diffuse into the bloodstream. In effect, diffusion across the dialysis membrane takes the place of normal glomerular filtration, and the characteristics of the dialysis fluid ensure that important metabolites remain in the bloodstream rather than diffusing across the membrane.

Table 2 Manifestations of the uremic syndrome *(6, 60)*

Acid-base balance and homeostatis
- Water retention : edema, congestive heart failure, acute pulmonary edema
- Hyponatremia
- Hyperkalemia
- Hyperphosphatemia
- Hypocalcemia
- Hypermagnesemia
- Metabolic acidosis

Neurologic

Central
- Daytime drowsiness and a tendency to sleep progressing to increasing obtundation and eventual coma
- Decreased attentiveness and cognitive tasking
- Imprecise memory
- Slurred speech
- Asterixis and myoclonus
- Seizures
- Disorientation and confusion

Peripheral
- Sensorimotor peripheral neuropathy, often with burning dysesthesia
- Singultus
- Restless leg syndrome
- Increased muscle fatigability and muscle cramps
- Postural hypotension

Cardiovascular
- Hypertension
- Accelerated atherosclerosis
- Cardiomyopathy
- Pericarditis

Gastrointestinal
- Anorexia progressing to nausea and vomiting
- Stomatitis and gingivitis
- Parotitis
- Peptic ulcer diathesis
- Gastritis and duodenitis
- Enterocolitis
- Pancreatitis
- Ascites

Pulmonary
- Atypical pulmonary edema
- Pneumonitis
- Fibrinous pleuritis
- Pulmonary fibrosis

Dermatologic
- Pruritus
- Dystrophic calcification
- Changes in skin pigmentation

Hematologic
- Anemia
- Altered neutrophilic chemotaxis
- Depressed lymphocyte function
- Bleeding diathesis with platelet dysfunction

Endocrinologic
- Secondary hyperparathyroidism
- Carbohydrate intolerance due to insulin resistance
- Type IV hyperlipidemia
- Altered peripheral thyroxine metabolism
- Testicular atrophy
- Ovarian dysfunction with amenorrhea, dysmenorrheal, dysfunctional uterine bleeding, cystic ovarian disease

Ophthalmic
- Conjunctival or corneal calcifications
- Retinopathy

Table 3 The composition of dialysis fluid compare to plasma fluid *(51, 54)*

Component	Plasma	Hemodialysis	Peritoneal dialysis
Electolyte			
Potassium (mEq/L)	4	2	0
Bicarbonate (mEq/L)	27	25-40	-
Phosphate (mEq/L)	3	-	-
Sulphate (mEq/L)	0.5	-	-
Nutrient			
Glucose (mg/dL)	80-100	0-200	140-390
Nitrogen waste (mg/dL)			
Urea	20	-	-
Creatinine	1	-	-
Uric acid	3	-	-

4.1 Hemodialysis

This process is undergone be means of a dialysis machine (Figure 2). As indicated in the several books *(52, 54)*, silicon rubber tubes called shunts are inserted into a medium sized artery and vein, typically located in the forearm. The connection of the two shunts acts like a short circuit that does not impede the flow of blood, and the shunts can be used to connect the individual to a dialysis machine. For long-term dialysis, a surgically created arteriovenous anastomosis provides access. During hemodialysis, the hemodialysis machine pumps bloods from the patients through a dialysis cartridge. Solutes diffuse between the blood and a dialysis solution, and then this results in the removal of metabolic waste products and the renewal of body buffer *(62)*. In dialysis cartridge, there is an artificial dialyzer, which consists of small units made up of finely extruded hollow fiber. High-flux dialysis membranes have a larger pore size. These are more efficient at removing larger solutes with molecular weights in the range of 1,500 to 5,000 *(62)*, but also fluid *(61)*. The use of high-flux dialyzers shortens the time required for dialysis and offers the advantage of improved blood purification by removing the higher molecular weight solutes *(62)*. In the dialyzer, the patient's blood is exposed to the dialysis solution across a semipermeable membrane. The blood is then pumped back to the patient through a return circuit. Treatment schedules are typically 3-5 hours three times a week. Despite the many technical advances in hemodialysis technology, patients undergoing this treatment continue to have a mortality rate of 5-10% while on maintenance dialysis *(54)*. When connected to the dialysis machine, the individual sits quietly while blood circulate from the arterial shunt, through the machine, and back through the venous shunt. In the machine, the blood flows within a tube composed of dialysis membrane, and diffusion occurs between the blood and the surrounding dialysis fluid.

Dialysis techniques can maintain patients who are awaiting a transplant, as well as those whose kidney function has been temporarily disrupted. Nevertheless, hemodialysis does have drawbacks, which are *(51)*

(1) Patients have to sit by the machine about 15 hours a week,
(2) During treatment, the symptoms of uremia gradually appear,
(3) Hypotension can develop as a result of fluid loss during dialysis,
(4) Air bubbles in the tubing can cause an embolism to form in the bloodstream,

(5) Anemia commonly develops, and
(6) The shunts can serve as sites of recurring infections.

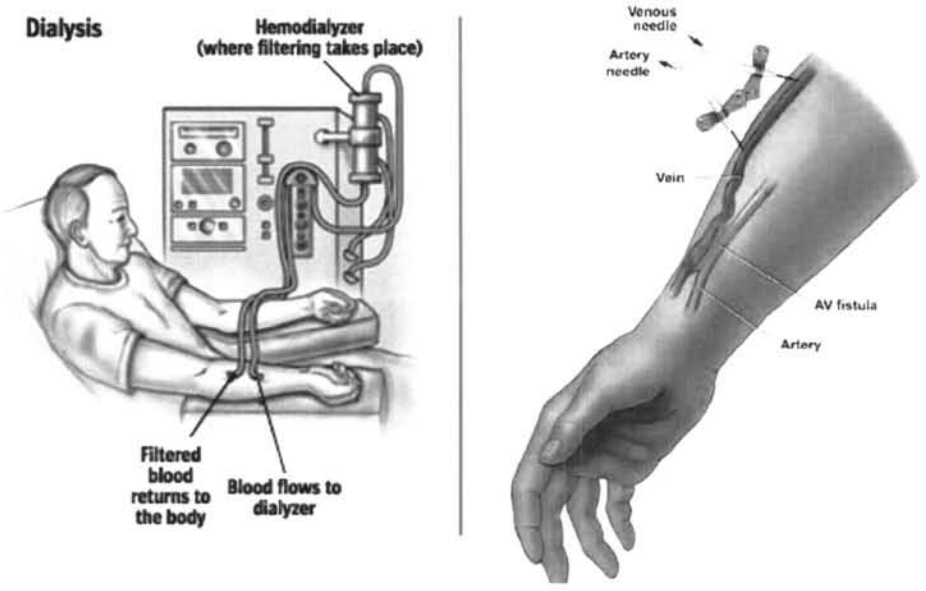

Figure 2 Hemodialysis. A patient is hooked up to a dialysis machine (left). Arteriovenous fistula (AV fistula) shown (right)

4.2 Peritoneal dialysis

One alternative to the use of a dialysis machine is peritoneal dialysis (PD), in which the peritoneal membrane is used as a dialysis membrane. Dialysis fluid is introduced into the peritoneum through a catheter in the abdominal wall (Figure 3).

4.3 Kidney transplantation

Probably the most satisfactory selection is kidney transplantation *(51)*. This procedure involves the implantation of a new kidney obtained from a living donor, or from a cadaver (Figure 3). The success rate for kidney transplantation varies; however, it depends on how aggressively the recipient's T cells attach the donated organ and whether an infection develops. Immunosuppresive drugs, therefore, are administratered to reduce tissue rejection, but unfortunately, this treatment also lowers the individual's resistance to infection.

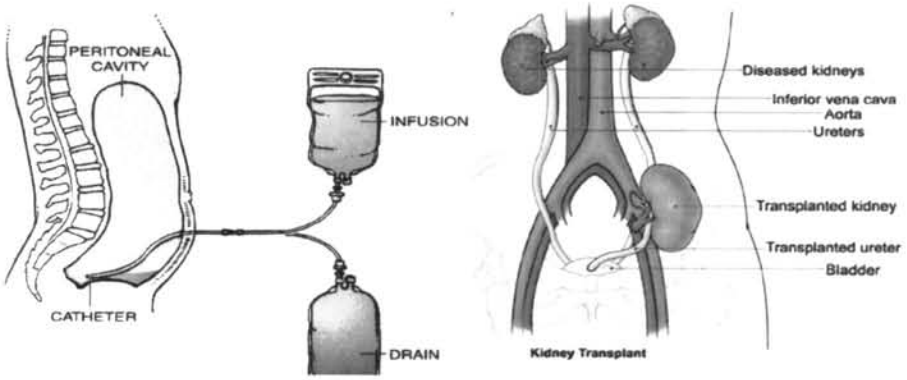

Figure 3 Peritoneal dialysis (left) and kidney transplantation (right)

5. Complications of Hemodialysis

Common complications are listed in Table 4. Although hemodialysis is a relatively safe procedure, a number of complications may still arise. The most common complications during hemodialysis are, in descending order of frequency, hypotension (20%-30% of dialysis), cramps (5%-20%), nausea and vomiting (5%-15%), headache (5%), and fever and chill (less than 1%) *(54)*

Hypotension is the most common adverse event during dialysis. Ultrafiltration-induced volume depletion is the most important cause *(61)*. The average blood pressure is below 100 mmHg or systolic blood pressure is 20-30 mmHg less than baseline, resulting from excessive or unduly rapid decreases in the blood volume *(63)*. This symptom usually takes place during dialysis-called intradialytic hypotension. It is a reflection of the large amount of fluid relative to the plasma volume that is removed during an average dialysis session. A decrease in the blood volume results in decreased cardiac filling, which causes reduced cardiac output and, ultimately, hypotension.

Muscle cramps The pathogenesis of muscle cramps during dialysis is unknown. However, there are three predisposing factors, which are hypotension, the patient's being below dry weight, and use of low sodium dialysis solution *(61, 64)* .

Nausea and vomiting These symptoms result from several factors. Most symptoms of them in stable patients are related to hypotension. Nausea or vomiting also can be an early manifestation of the disequilibrium syndrome .

Disequilibrium syndrome is a set of systemic and neurologic symptoms often associated with characteristic electroencephalographic findings that can occur either during or following dialysis. Early manifestations including nausea, vomiting, restlessness, and headache may prevent more serious symptom such as seizures, obtundation, and coma *(61, 65)*.

Dialyzer reactions include both anaphylactic and adverse reactions of unknown cause. About two-thirds of patients with anaphylactic reactions were found to have elevated serum titers of immunoglobulin E (IgE) antibodies to ethylene oxide, used to sterilize almost all hollow fiber dialyzers. Ethylene oxide hypersensitivity reactions were observed exclusively during first use of dialyzers. Recently, manufacturers have tried to remove most residual ethylene oxide from dialyzers, and some have changed the composition of the potting compounds to reduce absorption of ethylene oxide during sterilization *(62, 63)*.

Arrhythmia is especially common in patients receiving digitalis *(61, 63)*.

Air embolism These depend to an extent on the position of the patient. In seated patients, infused air tends to migrate into the cerebral venous system without entering the heart, causing obstruction to cerebral venous return, with loss of consciousness, convulsions, and even death. In recumbent patients, the air tends to enter the heart, generate foam in the right ventricle, and pass into the lungs. At this point, dyspnea, cough, and chest tightness can be expected *(61)*.

Dialysis-associated hypoxemia The fall in oxygen in arterial blood may be deleterious in a patient with sever preexisting pulmonary or cardiac disease.

Infection of vascular access site is usually manifested by fever with little or no sign of local inflammation. Vascular access-related infection can be caused by *Staphylococcus epidermidis* and *Staphylococcus aureus (65, 66)*. However, femoral catheterization can be affected by gram negative bacilli more often.

Table 4 Complications of hemodialysis *(61)*

Intradialytic hypotension
Cardiac arrhythmias as a result of rapid electrolyte change
Muscle cramps, nausea, vomiting
Need for rapid fluid removal
Disequilibrium syndrome
Anaphylactoid reaction (rare)
Activation of complement components
Endotoxin reactions from dialysate especially with high-flux dialyzers
Hypoxemia related to acetate use as a buffer
Rupture of dialysis membranes-blood loss
Air embolus from defective blood circuit and monitoring devices
Hepatitis Band C risk
Infection of dialysis access catheters

6. Malnutrition and muscle wasting in hemodialysis patient

Patients with chronic renal failure, and particularly those undergoing maintenance hemodialysis, frequently show evidence of wasting or protein-energy malnutrition (PEM) *(7, 9, 61)*. However, some authors prefer the phrase 'protein wasting syndrome' because not all causes of PEM are the result of inadequate nutrient intake *(67)*. PEM is one of the most potent predictors of mortality in hemodialysis patients. Large-scale studies have demonstrated that the nutritional state of a patient with hemodialysis therapy has a major impact on long-term survival *(68)*. Estimates of the prevalence of malnutrition vary, but on average about 40% of patients have mild to moderate malnutrition while approximately 10% suffer from severe malnutrition *(61, 69)*. In additon, it has been reported that maintenance dialysis patients experience a unique form of protein and energy malnutrition, which is characterized by muscle wasting and decreased visceral protein stores *(70-73)*.

The relationship between poor nutritional status and patient mortality rates has recently received much attention. Evidence from large groups of hemodialysis patients shows that mortality rates are higher in patients with low serum concentrations of albumin *(7)*. Patients with inadequate protein intake are at risk for developing malnutrition, and have a high morbidity and mortality *(74)*. Factors contributing to PEM in hemodialysis patients include anorexia, associated with uremia, advanced age, medication, or intercurrent illness such as depression, economic constraints, and the catabolic stress of the hemodialysis technique itself. One of the predictors for malnutriton is serum albumin, which relates to mortality risk. The study among hemodialysis patients with serum albumin levels between 3.5 and 4.0 g/dL have reported that these patients have two times greater mortality risk compared to those with value above 4 g/dL *(75)*. With serum albumins of 2.5-3.0 g/dL, mortality risk is increased 16-fold *(75)*.

A significant number of patients on hemodialysis ingest too little protein and calories to maintain lean body mass (LBM), and it results in muscle wasting and reduction of concentrations of visceral proteins such as albumin and transferrin *(56, 76)*. The changes are summarized in Table 5.

Table 5 Evidences for protein-energy malnutrition in patients with advanced chronic renal failure *(67, 77)*

Anthropometry and body composition	Biochemistry
• Body weight : continuous decrease or low percent of ideal body weight (< 85%) • Abnormal skinfold thickness, Muscle mass (mid-arm muscle circumference) • Abnormally low lean body mass by BIA and/or DEXA • Low total body nitrogen and/or nitrogen index (ratio of observed nitrogen and predicted nitrogen)	• Serum o Albumin < 4.0 g/dL o Transferrin < 200 mg/dL o Prealbumin < 30 mg/dL or an apparent decreasing trend o IGF-1 < 200 ng/mL • Altered profiles or abnormally low plasma and muscle amino acid concentration such as leucin, valine isoleucine, tyrosine, and total tryptophan • Relatively low serum creatinine level with other signs of uremia or low creatinine kinetics

BIA = bioelectrical impedance analysis, DEXA = dual energy X-ray absorptiometry, IGF-1 = insulin-like growth factor-1

Although the pathogenesis of PEM in hemodialysis patients is multifactorial, the decrease in protein and energy intake plays a particularly important role*(69)*. Predialysis restrictive diet, for example, is one of the causes resulting in PEM. It is because before starting hemodialysis, patients are prescribed low protein and low-phosphate diets. These diets, therefore, cause hypocaloric and may be deleterious to the patient's nutritional status *(78)*. Besides, hemodialysis patients require much greater protein and energy than healthy persons because of dialytic losses of amino acids *(9, 79)*. It has been reported that 4 to 9 grams of free amino acid are lost during the procedure through the dialyzer during fasting and 8 to 10 grams if patients are eating *(78)*. Other causes are listed in Table 6.

Table 6 Possible contributing factors of protein energy malnutrition in hemodialysis patients *(9, 11, 78, 80)*

Factors	Causes
• Predialysis restrictive diets	- low protein and low-phosphate diets
• Indequate nutritional intake	- taste abnormalities (acuity, metal flavor, and dry mouth) - gastropathy and enteropathy - accumulation of anorectic factors - inflammation and infection - medications - psychosocial factors - HD-related factors
• Dialysis-related nutrient loss	- free amino acids are lost during dialysis session
• Alteration in protein metabolism	- increased protein catabolism
• Inflammation	- markedly increased resting energy expenditure, and comorbid conditons.

6.1 In order to assess nutritional status, patient interview, assessment of food intake, medication intake, physical examination, bioimpedance, and laboratory tests should be taken. The methods for nutritional assessement are described in Table 7.

- **Patient interview**: to gather any symptoms of nausea, vomiting and anorexia, and also recent changes in body weight. It should be evaluated carefully to ascertain their cause.
- **Assessment of food intake**: to recall patient of food intake, determined on both dialysis and nondialysis days which can provide information on the intake of proteins, fats and carbohydrates.
- **Medical intake**: to determine the cause from any medications that can result in loss of appetite in patient. For example, aluminum-containing antacids, which are used for minimizing phosphate or iron supplement used for anemia, can be responsible for dyspepsia in patient. Additionally, prednisolone, other catabolic steroids and tetracyclines can increase protein catabolism after administration.
- **Physical examination**: to estimate nutritional status by comparing ideal to actual body weight and by evaluating the condition of mucous membranes, hair and skin. The method of this examination, which is mostly used to assess nutritional status, is anthropometry *(81)*. This method can provide a reasonably accurate value for assessing body fat and protein store. Because it is convenient, inexpensive, noninvasive, and unlimited, it is widely used by physicians. Anthropometry consists of height, weight, body mass index, skinfold thickness, and circumference measurement. The skinfold thickness measured at the biceps or triceps provides an estimate of body fat, whereas mid-arm circumference can be used to approximate of muscle mass. This measure can be compared to reference ranges established in well-nourished dialysis patients. However, as it may be influenced by hyperhydration, the routine use of these measurements cannot be recommended.
- **Bioimpedance**: to analyze body composition based on the measurement of resistance and reactance when applying a constantly alternating electrical current to a patient. The predictive total body mass is shown in phase angle, which is correlated with other predictors of nutritional status, such as anthropometric measurement and serum albumin levels.
- **Laboratory test**: to assess the nutritional state with respect to laboratory results. Biochemical values used for evaluation of protein status *(81)* in patients as following
  - Serum albumin Albumin is the most abundant of serum protein, which is also the most readily available for clinical assessment *(82)*. Serum albumin level has been shown to be an indicator of depleted protein status and decreased protein intake. Low concentration of albumin level leads to high morbidity and mortality in hospitalizing patients; it is shown that for every 1 gm/L decrease in albumin, a 10% increase in mortality risk has been reported *(83)*. A level less than 3.5 g/dL is considered an indicator of malnutrition *(78)*. However, some authors indicated serum albumin level less than 4.0 g/dL as malnutritional state *(84)*. The usefulness of a low serum albumin as a marker of mortality may reflect either nutritional deficiencies or the presence of an active inflammatory process. Hence, identifying and correcting reversible causes of malnutrition are essential to maintaining adequate nutrition in patients with ESRD. However, various factors can affect the value of albumin; for example, a 20-day half-life of albumin and large body pool (4-5 gram/kg of body weight) can result in serum levels to respond slowly to nutritional

change. Thus, albumin level is considered to be a poor indicator of early protein depletion and repletion *(82)*.

- Serum transferrin Serum transferrin is synthesized in the liver and binds and transports iron in plasma. Due to its smaller body pool and shorter half-life, it has been considered a better indicator of change in protein status compared with albumin. A value of less than 200 mg/dL is a marker of malnutrition *(84)*. Nevertheless, the use of transferrin as an index of nutritional status is limited by several factors. A factor that causes increased transferrin level is iron-deficiency anemia *(6, 85)*. On the other hand, factors like iron dextran administration *(6, 85)*, chronically draining wounds, traumas and uremia decrease transferrin levels *(82)*.
- Prealbumin Transthyretin- and thyroxin-binding prealbumin serves as a transporter for thyroxin (T_4) and as a carrier protein for retinol-binding proteins. Like transferrin, prealbumin has short half-life (2-3 days) and small body pool (0.01 gram/kg body weight) *(84, 86)*; it is therefore considered to be a more sensitive indicator of protein nutriture and to respond more rapidly to changes in protein status than albumin and transferrin *(6, 86)*. Serum prealbumin levels less than 30 mg/dL are associated with increased morbidity and mortality *(83, 84)*. Yet, patients with chronic renal failure who are on dialysis can show increased prealbumin due to decreased renal catabolism *(82)*. Moreover, other factors like insulin-like growth factor-1, and fibroretic can be used to assess nutrition deprivation as well *(6)*.

Since the landmark studies of Sargent and Gatch relating the measurement of the dose of dialysis using urea concentration with patient outcome, the delivered dose of dialysis has been correlated with morbidity and mortality. Inadequate dialysis shortens survival and leads to malnutrition, anemia, and functional impairment, causing frequent hospitalizations that increase the cost of health care. Besides, inadequate dialysis is often undetected unless it is severe and prolonged. Such features suggesting inadequate dialysis are urea reduction ratio *(87)* and Kt/V, but Kt/V has become the preferred marker for dialysis adequacy. Currently, a urea reduction ratio (URR) of 65% and a Kt/V of 1.2 per treatment are minimal standards for adequacy among ESRD patients *(56)*. As described above, the delivery of a dialysis dose that is less than adequate, as defined by National Kidney Foundation Dialysis Outcomes Quality Initiative guidelines *(59)*, results in the patient having a difficult time achieving the recommended levels of protein and energy intake. It is suspected that the provision of adequate dialysis corrects subtle uremia and thus enables patients to have less anorexia.

Table 7 Assessment of protein-energy malnutrition *(4)*

Methods to assess nutrition used in hemodialysis patients
Evaluation of Nutritional Intake
• Dietary history and dietary records
• Urea appearance (estimation of protein intake)
Simple Anthropometric Methods
• Body weight, body mass index, weight loss
• Skinfold thickness (triceps and other sites)
• Mid-arm muscle circumference (MAMC)
• Muscle strength (handgrip)
Body Composition
• Dual energy x-ray absorptiometry (DEXA)
• Nuclear magnetic resonance
• Computed tomography
• Ultrasonography
• Bioelectrical impedance analysis (BIA)
• Total body H20 (isotope dilution), K (40K-count), N (neutron activation analysis)
Biochemical Methods
• Plasma proteins (albumin, prealbumin, transferrin, IGF-1, complement C3, others)
• Other plasma and blood chemistries (hemoglobin, urea, creatinine, lipids, amino acids)
• Urea appearance
• Creatinine output
• Muscle alkali-soluble protein/DNA, RNA, amino acids (percutaneous biopsy)
Immunologic Methods
• Total lymphocyte count
• Delayed hypersensitivity skin tests

Nutritional assessment is a complex procedure including anthropometric, biochemical, and functional measurements *(41)*. However, it must be recognized that none of the variables currently used for nutritional assessment is a pure indicator of nutritional status because both hydration and the inflammatory response may significantly alter nutritional indices irrespective of changes in true nutritional status.

The following table presents a number of clinical studies using a variety of experimental designs, which have established the relationship between the effect of hemodialysis and muscle wasting in end-stage renal disease patients (Table 8).

Table 8 Changes in anthropometry and biochemical parameters in studies of effect of dialysis on end-stage renal disease patients

Author, *(reference)*	Number of study group (n)	Outcome of trial
Lee et al., *(47)*	26	• Skinfold thickness was significantly reduced ($p<0.001$)
Takahashi et al. , *(71)*	46 (28m/18f)	• Lean body mass and bone mineral content decreased while body fat increased
Gomez et al., *(88)*	32 (17m/15f)	• 40% of patients were at risk of protein-caloric malnutrition and more frequently muscle wasting in male while more fat depletion in female
Cohen et al., *(72)*	100	• 19% had sustained CK elevation with the skeletal muscle isoenzyme (CK-MM) predominating • Positive correlation between CK-MM and pre-dialysis BUN mean ($r = 0.52$, $p < 0.001$)
Svarstad et al., *(89)*	22 (14 HD, 8 PD)	• Thigh muscle area was reduced in HD and PD patients ($p < 0.01$ and $p < 0.05$ respectively) compared with normal group
McIntyre et al., *(73)*	134 (60 HD, 28 PD, and 46 CKD stage 4)	• Patient on maintenance dialysis exhibited more significant muscle wasting than patients with CKD stage 4 ($p < 0.001$)
Kato et al., *(90)*	262 (177m/85f)	• Limb/trunk lean mass ratio was significantly reduced in the expired group ($p < 0.01$)
Carvounis et al., *(91)*	22 HD	• Increased fat ($p<0.001$) while lean body mass, measured by MAMC significantly decreased ($p< 0.002$)
Jager et al., *(70)*	132 HD	• Serum albumin level significantly decreased ($p < 0.05$)
Lee et al., *(92)*	10,304 HD	• 70% of patients undergoing hemodialysis were classified based on body mass index as underweight and normal weight (BMI < 22.9 kg/m^2)
Jha et al., *(93)*	162 ESRD (142m/20f)	• Body mass index was lower in ESRD patients compared to male and female healthy subjects ($p<0.01$ and $p<0.05$ respectively) • A significantly lower fat mass percentage in male group ($p<0.0001$) as well as in female group ($p < 0.007$) compared to normal subjects

CK = creatine kinase, f = femal, m = male

7. Disorder of Carbohydrate Metabolism in Uremia

The previous study by Westervelt and Schreiner, using the forearm perfusion technique, showed that peripheral glucose uptake is reduced in uremic patients *(94)*. Also, the introduction of the euglycemic insulin clamp technique by DeFronzo et al. provided the opportunity to measure the amount of glucose metabolized per unit of insulin *(40)*. They examined uremic patients with the euglycemic clamp technique and the result indicated that tissue sensitivity to insulin is markedly impaired in uremia. Furthermore, the result also confirmed the primary site of the insulin resistance resides in peripheral tissue *(40, 95, 96)*. The study of Rigalleau and his co-workers revealed that insulin resistance is detectable when the glomerular filtration rate is below 50 mL/min/1.73 m^2 even in non-diabetic uremic individuals *(38, 97)*.

A multitude of abnormalities in carbohydrate metabolism is encountered in uremia (Table 9). Patients with chronic renal failure and those treated with hemodialysis almost always display resistance to the peripheral action of insulin *(38-40)*. The normal response of β (beta) cells to the presence of insulin resistance is to enhance their secretion of insulin. This is because the β cells are unable to augment their secretion of insulin appropriately; an impaired glucose tolerance would ensue. The increase in the blood levels of insulin in response to hyperglycemia in uremic patients may be decreased, normal, or increased. The liver and skeletal muscles are the major sites for peripheral uptake of glucose. However, the available data indicate that glucose metabolism by the liver is usually not impaired in uremia *(39, 40)*. Hepatic glucose production and its suppression by insulin are not altered in chronic renal failure *(40)*. Also glucose uptake by the liver is small and not affected by uremia *(40)*. Thus, it is apparent that the skeletal muscles are the primary site for the decreased sensitivity to insulin action *(40)*.

Abnormal glycemic control in end-stage renal disease has been detected even in nondiabetic patients, who often have mild fasting hyperglycemia and abnormal glucose tolerance manifested as abnormal glycemic responses during oral and intravenous glucose tolerance tests *(39)*. Insulin sensitivity can be reduced by up to 60% in nondiabetic patients with ESRD before dialysis *(98)*. Marked improvement in insulin sensitivity and glucose tolerance has been reported in nondiabetic ESRD patients after 10 weeks of hemodialysis; however, values did not normalize *(39, 99, 100)*.

Insulin resistance is thought to be one of the risk factors which can be detected in the course of renal failure and may contribute to the development of cardiovascular complications in these patients. Some evidences suggest that hyperinsulinemia may be an important risk factor for the development of atheroscelosis even in non-diabetic patients *(43)*. Likewise, some also reported that low insulin sensitivity is associated with coronary artery disease *(43, 44, 101)*.

Table 9 Characteristics of glucose and insulin metabolism in uremia *(96)*

- Normal fasting blood glucose
- Spontaneous hypoglycemia
- Fasting hyperinsulinemia[a]
- Normal, elevated, or decreased blood insulin levels in response to hyperglycemia induced by oral or intravenous glucose administration
- Elevated blood levels of proinsulin and C peptide
- Elevated blood levels of immunoreactive glucagon
- Impaired insulin secretion by pancreatic islets[b]
- Multiple derangements in metabolism and function of pancreatic islets
    - Impaired glycolytic pathways
    - Reduced basal and glucose-stimulated adenosine triphosphate content (ATP)
    - Elevated basal levels of cytosolic calcium
    - Decreased V_{max} of Ca^{2+} ATPase and Na^{+}-K^{+}-ATPase
    - Reduced calcium signal in response to glucose and potassium
- Normal hepatic glucose production
- Normal suppression of hepatic glucose production by insulin
- Decreased peripheral sensitivity to insulin action
- Impaired glucose tolerance[c]
- Decreased requirement for insulin by diabetic patients with diabetic nephropathy and uremia

[a]Normal blood insulin levels may be encountered.
[b]This is observed only in the presence of established secondary hyperparathyroidism.
[c]This is present only when insulin secretion is impaired in the presence of the commonly encountered resistance to the peripheral action of insulin.

Additionally, there is evidence showing the association between androgen and insulin resistance, which is well recognized from the study of Volpi and her colleagues *(45)*. They have conducted research in women diagnosed of hyperandrogenism showing that after surgical correction of hypertestosteronemia, lean body mass decreases and fat gains, particularly abdominal fat *(45)*. In addition, oral glucose tolerance test revealed moderate insulin resistance and glucose intolerance *(45)*. This research, thereafter, concluded that testosterone withdrawal worsened insulin sensitivity. The mechanism of the improvement of insulin sensitivity might relate to both directly and indirectly through changes in body composition*(45)*. However, this study is not unequivocally sensitizing, and sex or other characteristics may influence the response of glucose metabolism to testosterone.

7.1 Assessment of insulin resistance

Insulin resistance can be defined as a state in which normal amounts of insulin produce a suboptimal biological response. There are a number of tests used to assess the degree of insulin resistance. All of the investigative techniques have limitations and are not suitable for routine clinical use *(102)*. The most commonly used tests are the euglycaemic clamp and the homeostatic model assessment *(40, 100, 103)*. The hyperinsulinaemic euglycaemic clamp, which involves simultaneous infusions of insulin and glucose, is regarded as the gold standard. It is based on the principle that if glucose production by the liver is suppressed by an intravenous infusion of insulin then the amount of exogenous glucose required to maintain euglycaemia provides an estimate of the insulin sensitivity of target tissues (mainly skeletal muscle). This test

is useful for intensive physiological studies on small numbers of patients. However, insulin sensitivity can be determined from steady-state plasma levels of glucose and insulin by homeostatic model assessment (HOMA) *(50)*. HOMA is a simpler test and is more appropriate for large epidemiological studies. HOMA, described by Matthews et al.*(103)*, is a mathematical model by which values of insulin sensitivity can be calculated if simultaneous fasting plasma glucose and fasting insulin concentrations are known. It gives an estimate of basal insulin resistance, unlike other techniques, which measure stimulated insulin resistance. Assuming that normal subjects with normal weight have an insulin resistance of 1, the values for a patient can be calculated from the fasting concentrations of insulin and glucose using the following formula:

$$\text{Insulin resistance} = \frac{\text{fasting serum insulin } (\mu\text{U/mL}) \text{x fasting plasma glucose (mg/dL)}}{405}$$

7.2 The relationship of body fat and insulin resistance

Obesity, especially upper body obesity, is associated with insulin resistance *(45, 49, 104)* . BMI is traditionally used as an indicator of overall obesity. However, certain patterns of fat distribution are more closely related to increased incidence of diabetes and cardiovascular disease *(46)*. Abdominal or central obesity, as assessed by waist/hip ratio, is an essential component of metabolic syndrome and more strongly linked to the development of impaired glucose tolerance. Visceral fat, which constitutes a significant proportion of the intra-abdominal fat, has certain characteristic metabolic and anatomical features. The study by Chatchalit et al. *(105)* determined body fat distribution and its relationships with insulin sensitivity and cardiovascular risk factors in lean, healthy non-diabetic Thai subjects. It provided such a result as it was already mentioned, which is insulin sensitivity was inversely correlated with total body fat, abdominal fat, BMI and waist circumference in men (r=-0.636, r=-0.603, r=-0.556 and r=-0.529, $p<0.05$ for all variables); however, only total body fat were inversely correlated with insulin sensitivity in women (r=-0.561, p=0.03). This result by Chatchalit was resemble in the one by Toft *(104)*, which showed the significant negative relationships between the insulin sensitivity index and BMI (r=-0.59, p=0.0001). On the contrary, Dos Santos et al. studied in postmenopausal women to correlate body fat distribution to insulin resistance *(106)*. Analysis of the associations showed that HOMA-IR was the biochemical parameter that most explained the association with fat distribution; in addition, the correlation between waist circumference and HOMA-IR explained most of the variance in that association (R^2=34.9%, $p<0.001$).

Meanwhile, there are some data on the relationship between insulin resistance, and total body fat in non diabetic chronic kidney disease. Bancha and his coworkers concluded that in nondiabetic chronic kidney patients, the amount of total body fat is the independent factor for insulin resistance *(48)*. The correlation analysis of showed that HOMA-insulin resistance was positively correlated with percentage of total body fat in patients undergoing maintenance hemodialysis (r=0.27, $p<0.01$) *(48)* and in chronic kidney disease (r=0.32, $p<0.05$) *(48, 107)*.

Additionally, according to the study of Volpi and her colleagues, they summarized that androgens can influence body composition, which is indirectly associated with insulin sensitivity *(45)*. Thus, it is conceivable that androgens might indirectly influence insulin sensitivity via its effects on body composition. Also, the

study of Schroeder et al., which showed the decrements in abdominal fat after administration of oxymetholone 50 and 100 mg per day has confirmed that the changes in body composition, particularly increment of lean body mass and reduction of abdominal fat, can improve insulin resistance *(49)*. Similarly, Hobbs et al. conducted the study to clarify the impact of androgen on glucose metabolism *(108)*. All subjects were administered nandrolone decanoate for 6 weeks. They concluded that the treatment with anabolic androgenic steroid oes not aversely affect glucose metabolism.

7.3 Effect of Antihypertensive Therapy on Insulin Sensitivity

The effect of antihypertensive therapy on insulin sensitivity and secretion evolved from several reports that treated hypertensive individuals had a markedly increased risk of developing diabetes *(109-112)*. Middle-aged women treated for hypertension over a 12-year period with thiazides or propranolol were reported to have a five- to six fold greater risk of developing diabetes, while combination therapy increased the risk by a factor of nearly 12-fold *(113)*. The effect of various antihypertensive drugs on insulin sensitivity has been extensively studied by Lithell and his coworkers *(109)* . A summary of their salient finding is depicted in Figure 4. Both beta-blockers and thiazide diuretics worsen insulin resistance; calcium antagonists, such as the slow release of nifedipine, appear neutral in this regard *(111)*. In contrast, the angiotensin converting enzyme (ACEs) inhibitor such as captopril, and alpha$_1$-adrenergic antagonist, such as prazosin, improve insulin sensitivity *(109, 114, 115)*. Likewise, the effect of angiotensin II receptor antagonists (ARBs) such as olmesartan and valsartan on insulin sensitivity was investigated; they reported that olmesartan ameliorates insulin resistance as well *(116, 117)*. However, the study of Tillmann and Gress showed that captopril and enalapril do not modify insulin sensitivity in non-insulin dependent diabetic volunteers *(118, 119)*.

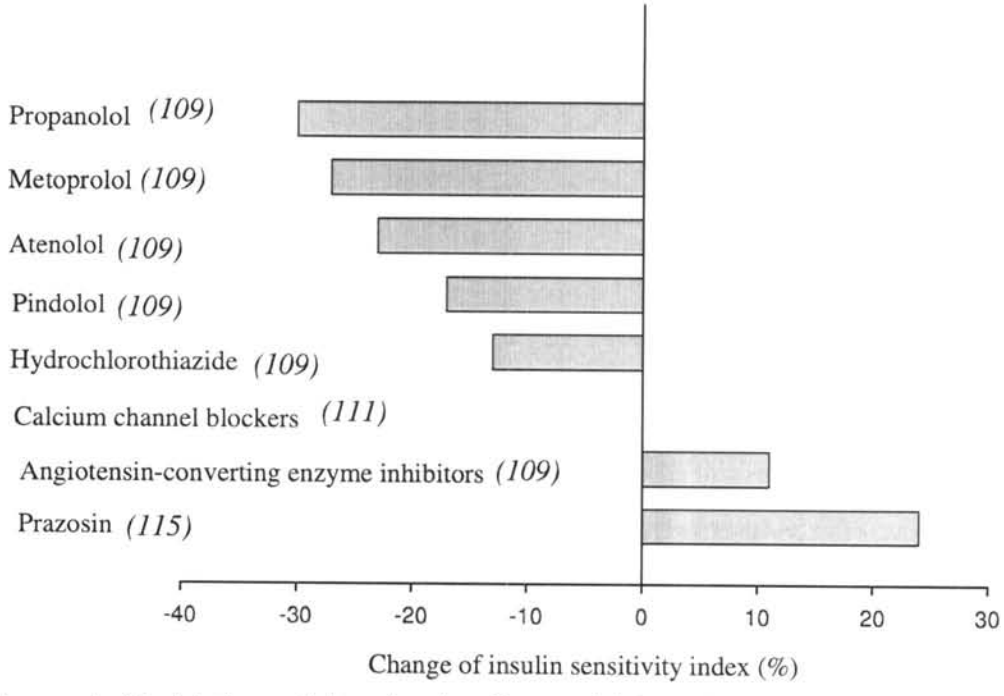

Figure 4 Modulation of *in vivo* insulin sensitivity with the use of various antihypertensive drugs. Adapted from Smith Ulf. Insulin resistance in hypertension

8. The Use of Anabolic Steroid in Medicine

With the isolation of testosterone in 1935, researchers began to explore potential applications of testosterone therapy based on its anabolic and androgenic properties. Since then, various studies of pharmacologic dose support the anabolic efficacy of the anabolic androgenic regimen. Clinical use of anabolic androgenic steroids (AAS) in eugonadal patients for anabolic benefit started in the 1940s. High-dose AAS regimens have been used to promote muscle deposition after burns, surgery, radiation therapy, and to treat hypogonadal men, age-related sarcopenia *(49, 120)*. Recent uses include treating wasting in human immunodeficiency virus (HIV) *(19, 23, 24, 121)*. However, cachexia is prevalent in a wide spectrum of chronic diseases, including chronic renal failure, hepatic cirrhosis, cancer, and pulmonary disease. Although increased caloric intake and an exercise regimen are of paramount importance in the maintenance of body weight, treatment with anabolic agents may enhance the effects of these measures. Some investigators attempted to apply the use of anabolic androgenic steroids in end-stage renal disease patients undergoing maintenance dialysis as in Table 10 *(13, 26, 122)*.

Early studies of orally or parenterally administered testosterone were unsuccessful, in part because rapid hepatic absorption and degradation via phase I metabolism resulted in subtherapeutic amounts of the hormone reaching target tissues *(29)*. To overcome this limitation, testosterone analogues were developed that had slower hepatic metabolism and produced longer systemic exposure. Further modifications were aimed at altering the anabolic-androgenic ratio for improving tolerability and efficacy, increasing *in vivo* half-life, and facilitating administration. This work resulted in the development of more than 120 synthetic testosterone analogues. The effects of these compounds were similar to those of testosterone: they increased nitrogen retention, stimulated erythropoiesis, and improved skeletal calcium uptake.

Anabolic androgenic steroids are synthetic derivatives of testosterone. All of them are androgenic as well as anabolic, but the modification of them is manufactured to maximize anabolic and minimize androgenic effects *(123)*. Anabolic androgenic steroid formulations may be administered orally, parentally by intramuscular injection, and transdermally by patch or topical gel *(124)*. Anabolic androgenic steroid was modified to retain anabolic androgenic potency, slow the rate of inactivation, change the pattern of metabolism, and decrease in aromatization to estradiol.

Most orally active anabolic androgenic steroid preparations are 17α-alkylated derivatives of testosterone that are relatively resistant to hepatic degradation. The common formulations of synthetic testosterone are shown in Table 11. For many years, scientists have labored to dissociate anabolic from androgenic effects with the hope of producing a purely anabolic agent that is free from any androgenic side effects. Unfortunately, no such compound exists. All of the listed drugs possess both anabolic and androgenic activity; none are absolutely selective. The relative ratios of testosterone derivatives are also shown in Table 11. The 17α-alkyl derivatives of testosterone constitute an important class of anabolic androgenic steroids (Figure 5). Introduction of the 17α-alkyl substituent into the testosterone molecule prevents metabolic inactivation through oxidation of the 17-hydroxy group to the 17-keto

group. This change slows metabolism of these compounds, increasing their efficacy when administered orally *(29, 125)*.

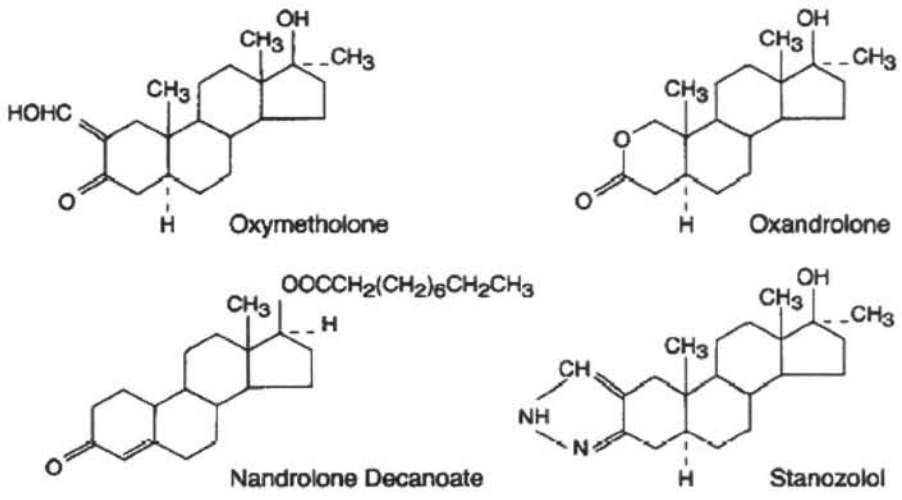

Figure 5 Structures of commonly used anabolic androgenic steroid

Many studies have shown that administration of androgens to hypogonadal and eugonadal young and elderly men results in an increase in lean body mass and strength *(46, 49, 125)*. AAS can also be anabolic in women who suffer from muscle-wasting as a result of disease *(121, 126)*. The direct mechanism of action of AAS is supposed that AAS increase efficient utilization of amino acids and increase androgen receptor expression in skeletal muscles. Indirect mechanisms are related to IGF-1, which needs androgens for the local production within the skeletal muscle regardless of the systemic IGF-1 levels and rate of growth hormone (GH) production *(12)*. Therapies that are currently available include AAS, megestrol acetate, GH, high calorie supplements, parenteral nutrition, and exercise. Therapy with megestrol acetate typically results in an increase in fat mass *(12, 14)* . GH use is associated with high cost and some untoward side effects *(12, 15)*, while treatment with oral essential amino acids and intradialytic amino acid supplementation offer no advantage compared to placebo *(127, 128)*. For this reason, other methods of treatment are in demand.

A number of previous studies show clear, statistically significant increase in muscle mass and strength after AAS administration *(13, 18, 49, 120-122, 129, 130)*. For example, in 1999 Johansen et al. conducted a double blind, placebo-controlled trial, 29 patients were randomized to either placebo or nandrolone decanoate (100 mg/week, intramuscular injection) for 6 months *(13)*. Serum creatinine and LBM were significantly greater in the nandrolone group. The results of functional tests such as timed walking and stair climbing also significantly improved in the nandrolone group, whereas, those results worsened in the placebo group. In 2006, Johasen et al. determined whether anabolic steroid administration and resistance exercise training induce anabolic effects among patients undergoing maintenance hemodialysis. It has been reported that patients who received nandrolone decanoate significantly increased their LBM ($p<0.0001$), whereas exercise did not result in a significant increase in LBM *(122)*. Moreover, nandrolone decanoate also has decreased fat mass in both men

and women *(13, 121)*. However, the use of nandrolone decanoate administered by intramusculare injection caused a hematoma at the injection site, but it resolved spontaneously *(13)*. Some of them appeared the rash skin that did not recover after the drug was discontinued; some had amenorrhea and acne *(13)*.

Mulligan et al. performed a study to examine the effect of nandrolone decanoate on weight and lean body mass in HIV-infected women with weight loss. This randomized, double-blind, placebo-controlled study was initiated with 38 HIV-infected women with documented weight loss to receive nandrolone decanoate 100 mg every other week by intramuscular injection for 12 weeks, followed by open-label therapy for 12 weeks. The results showed that subjects receiving nandrolone decanoate had significant increases in weight (4.6 kg) and lean body mass (3.5 kg) ($p<0.001$) *(121)*. The study of Demling in muscle-wasting from burn was establised to determine the effect of oxandrolone, a potent anabolic agent, compared to a nutrition support program on restoration of body weight and lean mass *(120)*. The results showed a significant increase in the amount and percent of LBM in the oxandrolone group *($p<0.05$)*. Futhermore, there was no change in body composition after six month discontinuation. All restored LBM was retained.

Table 10 provides a number of studies using physiologic and pharmacologic doses of protein anabolic agents, including growth hormone (GH), and anabolic androgenic steroids in patients with disease-related wasting.

Table 10 Studies of anabolic treatment with amino acid, recombinant human growth hormone (rhGH), exercise or anabolic steroids in disease-related muscle wasting patients

Author, *(reference)*	Number of study subject (n)	Study design	Intervention	Duration	Result
Johansen et al., *(13)*	29 HD	Randomized placebo-controlled trial	Nandrolone decanoate	24 weeks	• Increased lean body mass and serum creatinine ($p<0.01$, $p=0.02$, respectively)
Demling, et al, *(120)*	45 severe burns	Double blind, randomized placebo-controlled trial	Oxandrolone *vs.* nutrition-exercise program	At least 3 weeks	• Significant increase in body weight and lean body mass ($p<0.05$) in oxandrolone group
Mulligan et al., *(121)*	38 HIV (f)	Double blind, randomized placebo-controlled trial	Nandrolone decanoate 100 mg intramuscular injection	12 weeks	• Significantly increase in weight and lean body mass ($p<0.001$) • Fat mass did not change
Johansen et al., *(122)*	79 HD	2x2 factorial randomized placebo-controlled trial	Nandrolone decanoate intramuscular injection plus exercise	12 weeks	• Increased an average weight of lean body mass ($p<0.001$) • Decrease of fat mass ($p<0.01$)
Rammohan et al., *(14)*	10 HD (4m/6f)	Pretest-post test trial	Megestrol acetate 400 mg per day	16 weeks	• Increase in weight, body mass index, and triceps skinfold ($p<0.01$) • Increase in serum albumin ($p=0.03$)

Table 10 Studies of anabolic treatment with amino acid, growth hormone, or anabolic steroids in disease-related muscle wasting patients (continued)

Author, *(reference)*	Number of study subject (n)	Study design	Intervention	Duration	Result
Pupim et al., *(15)*	7 HD	Crossover	Recombinant human growth hormone (rhGH)		• Patient receiving rhGH lost less whole-body net protein balance ($p<0.05$) • Essential amino acid loss has significantly decreased
Hecking et al., *(127)*	13 HD	Double blind cross-over	Oral essential amino acid	12 weeks	• Increase in urea and uric acid ($p<0.05$)
Navarro et al., *(128)*	17 HD	Randomized placebo-controlled trial	Amino acid	12 weeks	• Significantly increased protein catabolic rate, serum albumin and transferrin ($p<0.05$ for all variables) • Anthropometric variables had not changed
MacDonold et al., *(131)*	9 HD	Pre tes*t*-post test trial	Exercise	12 weeks	• Physical function significantly improved ($p<0.05$) • Lean body mass unchanged ($p=0.536$)
Mulligan et al., *(132)*	79 HIV (m)	Double blind, randomized placebo-controlled trial	Megestrol acetate 800 mg plus testosterone enanthate 200 mg *vs.* biweekly megestrol acetate plus placebo	12 weeks	• No significant weight gain, lean body mass, and fat ($p=0.44$, $p=0.9$, and $p=0.11$, respectively)

9. Oxymetholone

Oxymetholone (17α-hydroxy-2-[hydroxymethylene]-17-methyl-5α-androstan -3-one) is an orally active 17α-alkylated anabolic-androgenic steroid. It was first synthesized by Ringold et al. in 1959 and introduced into clinical usage a few years later. Oxymetholone has been widely used in the treatment of anemia and in androgen therapy. Also, oxymetholone exhibits higher anabolic activity and lower androgenic activity than testosterone (Table 11).

Table 11 Anabolic androgenic ratios of anabolic androgenic steroids in animal models *(29, 125)*

Anabolic androgen steroid	Dosage form	Androgenic activity	Anabolic activity
Testosterone	IM	1	1
Oxymetholone	PO	0.45	3.2
Oxandrolone	PO	0.24	3.22
Nandrolone decanoate	IM	0.31-0.41	3.29-4.92
Stanozolol	PO	0.3	2.0-3.2

IM = intramuscular injection, PO = per oral

Currently, oxymetholone is approved by the US Food and Drug Administration (FDA) for the treatment of anemias caused by deficient red cell production. In addition, acquired or congenital aplastic anemia, myelofibrosis, and hypoplastic anemias due to the administration of myelotoxic drugs often respond to this medication *(29)*. Previously, researchers also have studied oxymetholone in the treatment of a variety of conditions, antithrombin III deficiency, growth impairment in children, and damaged myocardium in heart failure *(29)*. More recently, there have been demonstrations of clinical benefits of suprapharmacologic regimens suggests that such developments could be clinically beneficial. Many researchers are of interest in introducing anabolic androgenic steroids in muscle-wasting patients including HIV-associated wasting *(23-25)*. It has been proven that AAS improves lean body mass and reduces the fat redistribution syndrome, especially in HIV-wasting patients treated with protease inhibitors *(25)*.

Like nandrolone decanoate, oxymetholone is an oral anabolic androgenic steroid, which is proven to be able to promote lean body mass in muscle-wasting related to dialysis patient *(26)*. The use of nandrolone decanoate has drawback because of resulting hematoma, bacterial or fungal abscesses, and pain at the site of injection *(13)*. The increase of lean body mass has been obviously noticeable when using oxymetholone 100 mg per day in patient with continuous ambulatory peritoneal dialysis ($p<0.05$) *(26)*. Table 12 provides a number of studies using oxymetholone in patients with disease-related wasting.

Table 12 Studies on the effects of anabolic androgenic steroids and oxymetholone in disease-related muscle wasting patients

Author, (reference)	Number of study subject (n)	Study design	Intervention	Duration	Result
Hengge et al., *(24)*	89 HIV	Double blind, randomized placebo- controlled trial	Oxymetholone 50 mg	16 weeks	• Significant weight gain ($p<0.05$) • 100 mg oxymetholone appears to be equally effective as 150 mg in term of weight gain and is associated with less liver toxicity
Hengge et al., *(31)*	60 HIV	Prospective pilot study	Oxymetholone *vs.* oxymetholone plus ketotifen	30 weeks	• Increased average weight ($p<0.001$) • Improved quality of life ($p<0.05$)
Urbina et al., *(25)*	20 HIV	Open-label pilot study	Oxymetholone 50 mg once daily	24 weeks	• Increased body cell mass ($p=0.091$) • Increased fat free mass ($p=0.027$)
Ouppatham et al., *(26)*	20 CAPD	Double blind, randomized placebo- controlled trial	Oxymetholone 50 mg twice daily	24 weeks	• Increased lean body mass ($p<0.05$) • Increased body weight and body mass index (both $p=0.001$) • No serious adverse drug reaction was observed

9.1 Safety data

Since anabolic actions are not easily dissociated from the other actions of testosterone derivatives, anabolic steroid use by patients is inevitably accompanied by unwanted side effects that result from the many actions of androgens in the body. The common side effects of oxymetholone are likely the same as all anabolic androgenic steroids. They may cause androgenic side effects such as acne, due to stimulation of sebaceous glands in the skin, induced growth of facial hair in women, alopecia. In women using anabolic steroids for a prolonged period of time, masculinization may be manifested as hirsutism, deepening of the voice, decreased body fat, amenorrhea and menstrual irregularities that are caused by steroid use *(28)*. However, these side effects are reversible after drug discontinuation *(29, 125)*.

Moreover, the most severe adverse effect of AAS is related to liver function effects; hepatotoxicity. Elevations in aspartate aminotransferase *(62)*, alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) have been reported with AAS use. Cholestatic jaundice is the major hepatic side effect and is both dose and duration dependent *(24, 133)*. Anabolic steroids have been implicated in intrahepatic cholestasis. Jaundice usually develops after 2-5 months of therapy *(134)*. A small number of case reports have been published documenting the occurrence of cholestatic jaundice in patients treated with oxymtholone *(29)*. Functional liver failure and hepatic necrosis have not been observed with oxymetholone when a single agent was used. Although there have been some case reports of peliosis hepatic (unusual cystic lesion of the liver) in patients receiving oxymetholone, those patients had been exposed to other drug-induced liver toxicity before taking oxymetholone *(27)*. Hepatic enzyme elevations usually return to normal once the AAS are discontinued *(27, 30, 135)*. If the AAS are continued despite elevations in liver enzyme concentrations, dose-dependent cholestatic jaundice may occur. Hepatocellular carcinomas were more often associated with oxymetholone. There is an increased risk of peliosis hepatis with steroid use. This is a rare form of hepatitis characterized by formation of multiple blood-filled cysts within the liver, which can be fatal *(28)*. The adverse events found in the study of Hengge *(24)* showed liver-associated adverse events that occurs in the oxymetholone groups. Thirty-five percent of patients who received 150 mg oxymetholone developed abnormal liver function while 27% in the 100 mg oxymetholone group. Meanwhile non-liver-associated side effects commonly associated with the use of anabolic steroids was greater in the oxymetholone group compared to placebo (58% *vs.* 36%).

Besides, dyslipidemia may occur during the use of oxymetholone. It has been reported that marked hypertriglyceridemia and hypercholesterolemia occurred in patients following five and a half weeks of oral treatment with oxymetholone 100 mg/day *(33)*. In addition, a few studies reported that decreased high density lipoprotein cholesterol (HDL-C) can be observed in anabolic steroid group *(25, 30, 136-139)*. Likewise, after androgen therapy was discontinued, over one to three-month period, plasma lipid values progressively decreased below pretreatment values *(33, 34, 125)*. The pronounced effects on serum lipids and lipoproteins seem to be exerted by the oral 17α-alkylated steroids that is oxymetholone rather than parenterally administered nandrolone decanoate. Table 13 shows adverse effects of anabolic androgenic steroids used in medicine.

Table 13 Adverse effects of anabolic androgenic steroids

Author (*reference*)	Adverse effects		
	Androgenic effects	**Hepatic effects**	**Lipid effects**
Johansen et al. *(13)*	Amenorrhea (7%) Acne (7%)	Not reported	Not reported
Hengge et al. *(24)*	Acne (11-13%) Menstrual abnormalities (4%) Aloepecia (3%) Gynecomastia(1%)	Elevated liver enzymes (13-16%) Jaundice (19%) Hepatomegaly (not reported)	Not reported
Reeves et al. *(34)*	Not reported	Not reported	Increase in TG and Cholesterol
Choi et al. *(33)*	Not reported	Within normal limit	Increase in TG (67%)
Lovejoy et al. *(140)*	Not reported	Not reported	Decrease in HDL-C Increase in LDL-C

9.2 Drug metabolism and interaction

Thacker et al. *(141)* investigated the human metabolism of oxymetholone in human liver microsomes and recombinant human cytochrome P450 (CYP450) isoforms. They reported that no data exists on the CYP450 isoforms involved in the human metabolism of oxymetholone and so it is not currently possible to predict likely drug interactions that might result in toxicity or lack of efficacy. The results revealed that oxymetholone was able to inhibit the metabolism of prodrugs for CYP450 2D6 (such as dextromethorphan to dextrophan), CYP450 3A (such as dextromethorphan to 3-methoxymorphian). Also, both CYP450 2C9 (tolbutamide to 4-OH tolbutamide) and CYP450 2C19 (omeprazole to 5-OH-omeprazole) was inhibited. In addition, when oxymetholone was incubated with ritonavir, a known CYP450 3A substrate, there was weak competitive inhibition of ritonavir metabolism. Moreover, when it was incubated with human liver microsomes or recombinant CYP450 enzymes, oxymetholone metabolism occurred in a non-NADPH dependant manner, indicating that the primary route of oxymetholone metabolism is not via CYP450, consistent with the metabolism of other androgenic steroids such as testosterone. Ultimately, they concluded that oxymetholone interacts with human cytochrome P450s 2D6, 3A, 2C9 and 2C19, but is unlikely to cause clinically significant interactions at therapeutic doses.