1. Introduction and literature review

1.1Introduction:

Chronic renal failure (CRF) is a clinical syndrome that occurs when there is gradual decline of renal function over time. With renal failure there are many physiology derangement of homeostasis of water and minerals (sodium, potassium, chloride, calcium phosphate, magnesium, and sulphate). (Bishop, *et al.*, 2010).

In 2004 Chronic renal failure was found to be the 10^{th} cause of death in Sudan it accounts for about 2% of death. In 2005 the 6^{th} cause of death in sudan it accounts for about 4% of death this indicates the number of death due to Chronic renal failure is increasing.(Abeed,2005).

Chronic kidney disease is a world wide epidemic and escalating problem. Approximately 20 millions adults in the United States are in various stages of chronic kidney disease. (Coresh, 2003).

The gradual failure of kidney function is accompanied by metabolic abnormalities including disordered phosphorus and calcium metabolism. (Block, *et al.*, 2004)

Dialysis is used in cases of acute renal failure to improve the renal function, it may also used to prepare patient with chronic renal failure for transplantation, Dialysis to remove urea and other toxic substances from the plasma and correct electrolyte balance by dialyzing patient blood against fluid containing no urea and appropriate concentration of electrolytes, free ionized calcium and other plasma constituents. (Mayne, *et al*., 2000).

1.2Literature Review

1.2.1 Urinary system:

The paired kidneys lie on either side of the vertebral column be low the diaphragm and liver, each adult kidney weighs about 160 g and about11cm long and 5to7cm

Wide about the size of first, urine produced in the kidneys is drained into a cavity known as renal pelvis and then it is channeled from kidney via long ducts the ureters to the urinary bladder. (Ridge, 2006).

1.2.1.1 Kidneys:

the right kidney is at a lower level compared to the left ,the is kidney covered by the renal fascia and per renal fat ,these coverings long with the renal vessels ,the helium of the kidney is in the Tran pyloric plane about 5cm from the midline ,it is upper pole lies 2.5 cm and the lower pole 7.5 cm away from midline ,posterior the kidneys lie on the diaphragm the poses major the quadrates labarum and the transverses abdominals ,the cost diaphragm is an important posterior relation of the kidney. (Jacob, 2002).

1.2.1.2 The ureters:

the ureter lies on the psoas major muscle behind the parietal peritoneum to which it is adherent on both sides the ureters cross the genitofemoral nerves and are crossed by the gonadal vessels, the right ureter lies behind the third part of the duodenum and as it descends is crossed by the ilecolic vessels and the root of the mesentery. (Bishop, *et al*., 1985).

1.2.1.3 Urinary bladder:

The empty bladder has a superior surface; two infer lateral surfaces and abase the base faces posterior the lower part of the bladder which is continuous with the urethra is known as the bladder neck only the superior is covered by peritoneum. (Bishop, *et al*., 1985).

1.2.1.4 Urethra:

female urethra which is about 4cm long lies on the anterior wall of the vagina and opens in the vestibule between the anterior ends of the labia minor and the clitoris, male urethra is about 20 cm long having three parts, it passes through the prostate deep perineal push and then through the corpus spongiosum of the penis. (Bishop, *et al*., 1985).

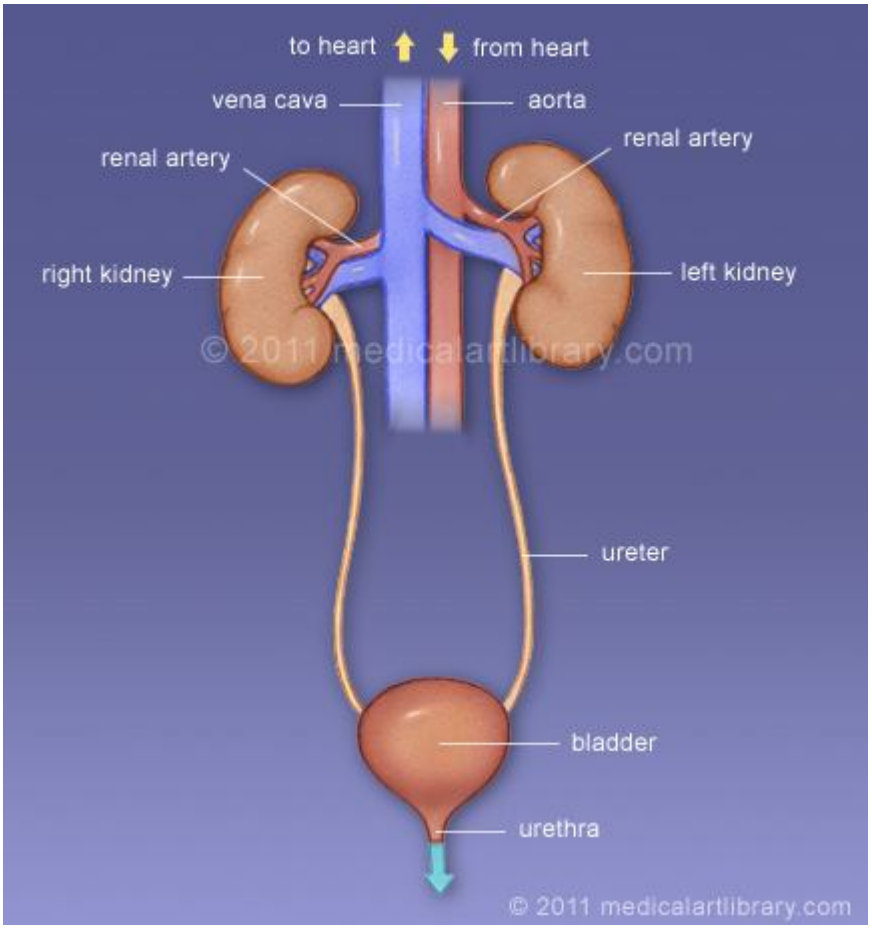

Figure (1.1): structure of Urinary System.

1.2.1.5 Renal physiology:

There are three basic renal processes:

- Glomerular filtration
- Tubular reabsorption
- Tubular secretion.

♣The Glomerular filtration:

The glomerulus is the first part of the nephron and functions to filter incoming blood Several factors facilitate filtration one factor is the unusually high pressure in the glomerular capillaries which is a result of their position between two arterioles. This sets up a steep pressure difference across the walls ,Another factor is the semi permeable glomerular basement membrane ,which has a molecular size cut off value of approximately 66,000 Dalton about the molecular size albumin .this means that water electrolytes and small dissolved solutes ,such as glucose ,amino acid ,low molecular weight proteins ,urea and creatnine pass freely through the basement membrane and enter the proximal convoluted tubule other blood convoluted tubule other blood constituents such as albumin many plasma proteins ,cellular elements and protein _bound substance such as lipids and bilirubin are too large to be filtered in addition ,because the basement membrane is negatively charged molecules such as proteins are repelled of the 1200_1500 ml of blood that kidneys receive each minute (approximately one quarter of the total cardiac out put) The glomerulus filters out 125_130 ml of an essentially protein _free, cell _free fluid per minute is the glomerular filtration rate (GFR) and it is determination is essential in evaluating renal function. (Bishop, *et al.*, 1985).

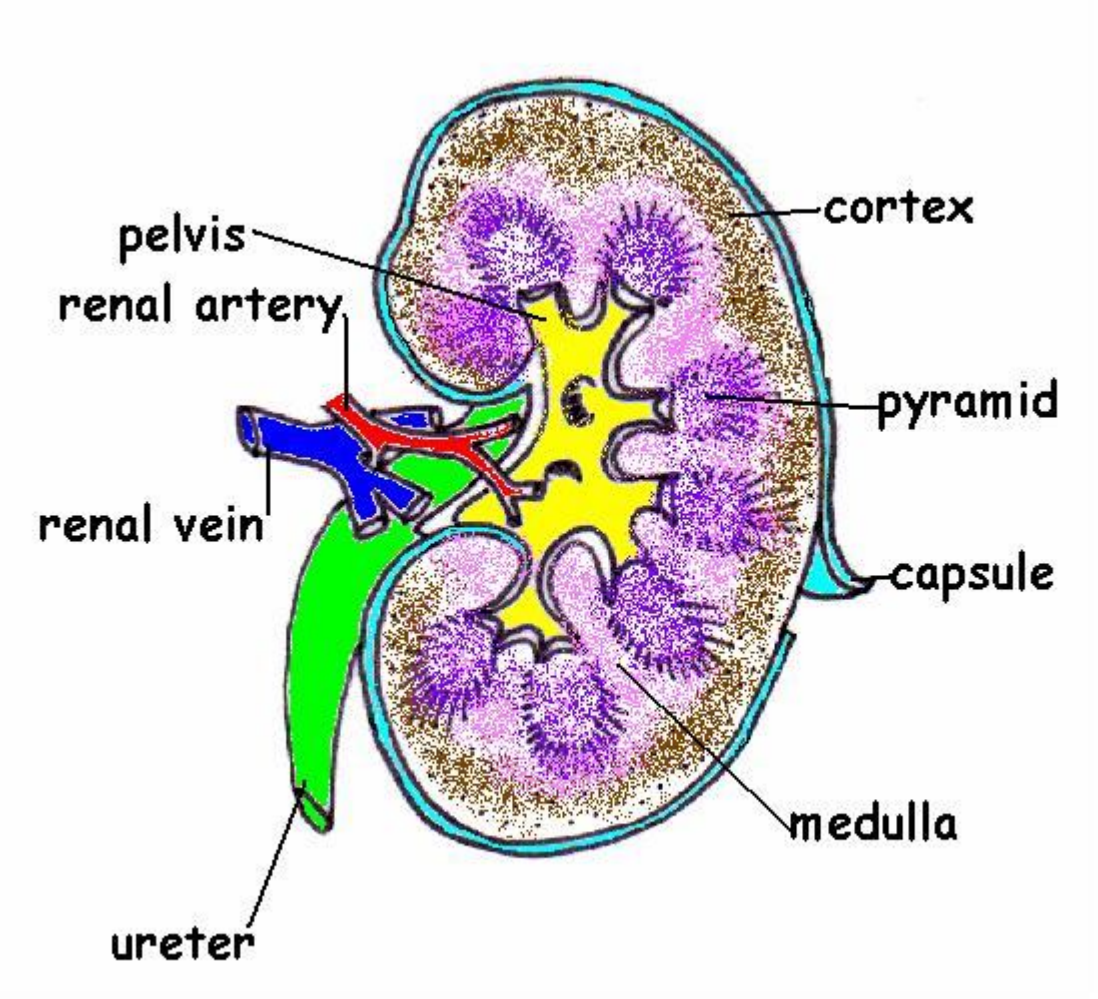

Figure (1.2) Structure of Kidney

♣Tubular Functions:

Proximal convoluted tubule:

The proximal tubule is the next part of nephron to receive the now cell _free and essentially protein free food .this filtrate contains waste products which are toxic to the body above a certain concentration and substances that are valuable to the body .one function of the proximal tubule is to return the bulk of each valuable substance back to the blood circulation .thus 75%of the water ,sodium and chloride ,100% of glucose up to the renal thre shold ,almost all of the amino acids vitamins and ions such as magnesium calcium, potassium and bicarbonate are reabsorbed .almost all (98% _ 100%) of uric acid a waste product is actively reabsorbed only to be secreted at the distal end of the proximal tubule ,when the substances move from the tubular lumen to the peritubular capillary plasma the process is called tubular reabsorption .with the exception of water and chloride ions ,the process is active that is the tubular epithelial cells use energy to bind and transport process that are involved normally have sufficient reserve for efficient reabsorption but they are saturable .when the concentration of filtered substance exceeds the capacity of the transport system ,the substance is then excreted in the urine the plasma concentration above which the substance appears in urine is known as the renal thre shold and it is determination is use ful in assessing both tubular function and non renal disease states. (Bishop, *et al.*, 1985).

A renal threshold does not exist for water because it is always transported passively through diffusion down diffuse in the wake of sodium.

Asecond function of the proximal tubule to secrete products of kidney tubular cell metabolism such as penicillin the term **tubular secretion** is used in two ways:

1-tubular secretion describes the movement of substances from peritubular capillary plasma to the tubular lumen.

2. Tubular secretion describes when tubule cells secrete products of their own cellular metabolism into the filtrate in the tubular lumen .transport across the membrane of the cells in again either active or passive. (Bishop, *et al.*, 1985).

1.2.1.5.1 Loop of Henle:

Counter current multiplier system:

The osmolality in the medulla in the portion of the nephron increases steadily from the corticomedulary junction in ward and facilitates the reabsorption of water ,sodium and chloride the hyperosmolality that develops in the medulla is continuously mainted by the loop of Henle ,a hairpin _like loop between the proximal tubule and the distal convoluted tubule .the opposing flows in the loop,the down ward flow in the descending limb ,and the up ward flow in the ascending limb is termed a countercurrent flow .to under stand how the hyperosmolality is mainted in the medulla it is best to look first at what happens in the ascending limb ,sodium and chloride are actively and passively reabsorbed into the medulla interstitial fluid along the entire length of the ascending limb.

Because the ascending limb is relatively impermeable to water, little water follows and medulla interstitial fluid become hyper osmotic compared with the fluid in the ascending Limb. (Bishop, *et al*., 1985).

1.2.1.5.2 Distal convoluted tubule:

The distal convoluted tubule is much shorter than the proximal tubule ,with two or three coils that connect to a collecting duct the filtrate entering this section of the nephron is close to it is final compostion .about 95% of the sodium and chloride ions and 90% of water have already been reabsorbed from the original glomerular filtrate .the function of the distal tubule is to effect small adjustments to achieve electrolyte and acid _base homestasis ,these adjustments occur under the hormonal control of both anti diuretic hormone (ADH) and aldosterone.(Bishop, *et al.*, 1985).

1.2.1.5.3 Collecting Duct:

The collecting ducts are the final site for either concentrating or diluting urine ,the hormones ADH and aldosterone act on this segment of the nephron to control reabsorption of water and sodium .chloride and urea are also reabsorbed here .urea plays an important role in maintaing the hyperosmolality of the renal medulla .Because the collecting ducts in the medulla are highly permeable to urea ,urea diffuse down its concentration gradient out of the tubule and into the medulla interstitum,increasing its osmolality. (Bishop, *et al.*, 1985).

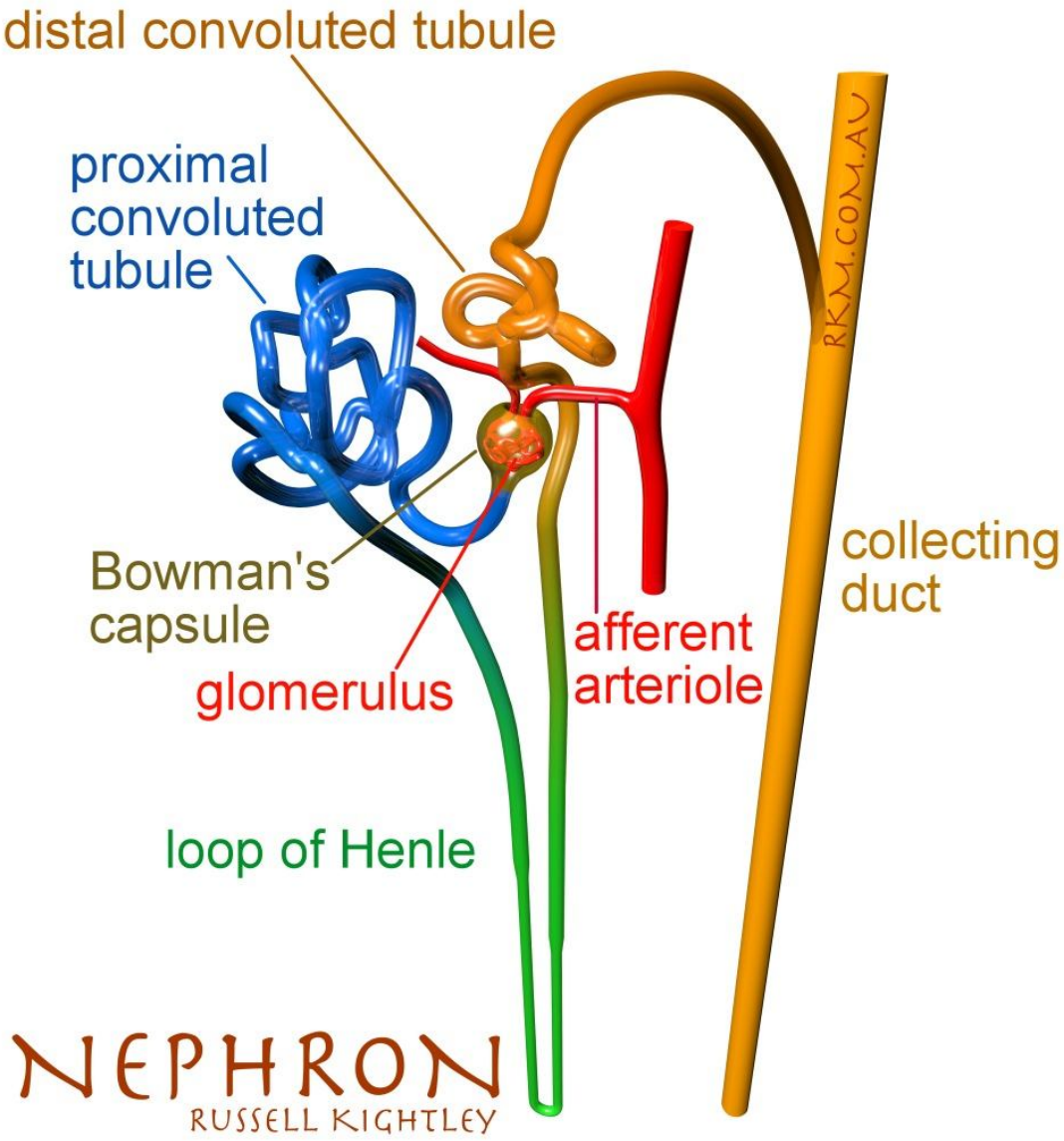

Figure (1.3): Structure of Nephron

1.2.2 Functions of the urinary system are :

Urine formation, fluid and electrolyte balance, regulation of acid _base balance excretion Of the waste products of protein metabolism, excretion of drugs and toxins
Secretion of hormones. (Bishop, *et al*., 1985).

1.2.3 Normal Functions of the Kidneys depend on:

- the integrity of the glomeruli and the tubular cells
- Abnormal blood supply under normal circumstances about20percent of the cardiac output flows through the kidney
- Normal secretion and feed back control of hormones acting on kidney. (Mayn, 1994).

1.2.4 Renal Failure:

1.2.4.1 Acute renal failure:

Is a sudden sharp decline in renal function as a result of an acute toxic or hypoxic insult to the kidneys defined as occurring when the GFR is reduced to less than 10 ml \min this syndrome is subdivided into three types dependining on the location of the precipitating defect. (Bishop, *et al*., 1985).

1.2.4.1.1 Pre renal failure:

The defect lies in the blood supply before it reaches the kidney causes can include cardiovascular system failure and consequent hypovolemia. (Bishop, *et al*., 1985).

1.2.4.1.2 Primary renal failure:

The defect involves the kidney the most common cause is acute tubular necrosis other causes include vascular obstruction, inflammation and glomerulonephritis. (Bishop, *et al*., 1985).

1.2.4.1.3 Post renal failure:

The defect lies in the urinary tract after it exist the kidney ,generally acute renal failure occurs as consequence of lower urinary tract obstruction or rupture of the urinary bladder Toxic insults to the kidney that are sever enough to initiate acute renal failure include hemolytic transfusion reactions ,myoloniuria due to rhabdomylosis ,heavy metal solvent poisonings antifreeze ingestion and analgesic and amino glycoside toxicities ,these conditions directly damage the renal tubules .hypoxic insults include conditions that

severely compromise renal blood flow such as septic hemorrhagic shock ,burns and cardiac failure ,the most commonly observed symptoms of acute renal failure are oliguria and anuria (<400 mg\dl) the diminished ability to excrete electrolytes and water results in significant increase in extra cellular fluid volume ,leading to peripheral edema ,hypertension and congestive heart failure ,most prominent however is the onset of the uremic syndrome or ESRD in which increased BUN and serum creatinine values are observed along with the preceding symptoms .the out come of this disease is either recovery or in the case of irreversible renal damage ,progression to chronic renal failure. (Bishop, *et al*., 1985).

1.2.4.2 Chronic Renal Failure:

Chronic kidney disease (CKD) is a clinical syndrome that occurs when there is gradual decline in renal function over time , according to the 2007 US ,Renal Data System (USRDS) Annual Data report one in nine US adults has CKD and 20 million more are at risk, early detection and treatment are needed to prevent progression to ESRD and complications such as coronary vascular disease .the national kidney foundation has formulated guidelines for earlier diagnosis ,treatment and prevention of further disease progression .GFR and evidence of kidney damage based on measurement of proteinuria or other markers form the basis of the classification The conditions that can precipitate acute renal failure also may lead to chronic renal failure. (Bishop, *et al*., 1985).

♣Diagnosis:

Chronic renal disease is identified by blood test for creatinine .Higher levels of creatinine indicate a falling glomerular filtration rate and as a result a decreased capability of the kidneys to excrete waste products. (Bishop, *et al*., 1985)..

1.2.4.3 Increasing Incidence of chronic kidney disease:

There is an increasing incidence of CKD in the US due to the increase in diabetes Diabetes mellitus can have profound effects on the renal system patients with type 1 diabetes have an insulin deficit approximately 45% of patients with type 1 diabetes will develop progressive deterioration of kidney function (Diabetic nephropathy)within 15_20years after diagnosis ,a smaller percentage of persons with type 2 diabetes will also develop this condition .the effects are primarily glomerular but they may affect all kidney

structures as well and are theorized to be caused by the abnormally hyperglycemic environment that constantly bathes the vascular system . (Bishop, *et al.*, 1985).

1.2.4.4.1Therapy of acute renal failure:

1- Dialysis:

In patients with acute renal failure, uremic symptoms uncontrolled hyperkalemia and acidosis have traditionally been indications that the kidneys are unable to excrete the body s waste products and substitute method in the form dialysis was necessary .Dialysis is often institute before this stage however several forms of dialysis are available however they all use a semi permeable membrane surrounded by adialysate bath. (Bishop, *et al.*, 1985).

In traditional hemodialysis (remove the waste from blood) the membrane is synthetic and outside the body, arterial blood and dialyzed are pumped at high rates (150_250ml \min) And 500 ml/min respectively in opposite directions. The blood is returned to the venous circulation and the dialysate discarded the diffusion of low molecular weight solutes (<500Da) into the dialysate is favored by the process but mid –molecular weight solutes (500_2000Da) are in adequately cleared creatinine clearance is about 150_160ml\min. (Bishop, *et al.*, 1985).

1.2.4.4.2Therapy of the End _stage renal disease

For patients with irreversible renal failure, dialysis and transplantation are the only two therapeutic options, initiation of either treatment occurs when the GFR falls to 5ml\min (10_15ml/min) in patients with diabetic nephropathy. (Bishop, *et al.*, 1985).

2-Dialysis:

traditional hem dialysis or it its more recent high efficiency form as well as peritoneal dialysis are the available methods the clinical laboratory used in conjunction with ahemodialysis facility must be able to adequately monitor procedural efficiency a wide variety of areas, renal dialysis has basic goals and specific laboratory tests should be performed to evaluate the achievement of each goal. (Bishop, *et al.*, 1985).

3-Transplantation:

The most efficient hemodialysis techniques provide only 10%_12% of the small solute removal of two normal kidneys and considerably less removal of larger solutes even patients who are well dialyzed have physical disabilities and decreased quality of life

Kidney transplantation offers the greatest chance for full return to healthy productive life however this option is limited by the significant shortage of donor organs for ESRD patients waiting for an organ donation can vary from several months to several years. (Bishop, *et al.*, 1985).

♣Non Protein Nitrogen Compounds:

Are waste products formed in the body as a result of degradative metabolism of nucleic acids, amino acids and proteins. Excretion of these compounds is an important function of kidneys. (Bishop, *et al*., 1985).

1- Uric acid:

Biochemistry and physiology:

In humans uric acid is the major products of the catabolism of the purine nucleosides,adenosine and guanosine ,purines from catabolism of dietary nuclic acid are converted to uric acid directly .how ever the bulk of purines ultimately excreted as uric acid in the urine arises from degradation of endogenous nucleic acids .the catabolism of purines is illustrated in out line ,reutilization of the major purine bases ,adenine hypoxanthine and guanine is achieved through (salvage) pathways in which phosphosribosylation of the free bases causes resynthesis of the respective nucleotide monophosphate.(Tietz,1987).

Uric acid metabolism:

Purine nucleotides are essential components of nucleic acid they are intimately involved in energy transformation and phosphorylation reactions and act as intracellular messengers there are three sources of purines in human, the diet degradation of endogenous nucleotides and denovo synthesis .since purines are metabolized to uric acid the body urate pool and hence concentration depends on the relative rates of both urate formation from these sources and urate excretion. (Marshall, *et al*., 2004).

Urate is excreted by both the kidneys and gut renal excretion accounting for approximately two_third of the total urate ammonia by bacterial action (uricolysis)

Urate handling by the kidney is complex, it is filtered at the glomeruli and almost totally absorbed in the proximal convoluted tubules, distally both secretion and reabsorption occur, normal urate clearance is about 10% of filtered load in normal subjects, urate excretion increases if the filtered load is increased. In chronic renal failure the plasma concentration raises only when the glomerular filtration rate falls below about 30%of excreted urate, the introduction of apurine _free diet typically reduces plasma urate concentrations by only 10 _20 %, the metabolic pathways leading to uric acid synthesis are shown is out line. (Marshall, *et al*., 2004).

Denovo synthesis leads to the formation of inosine monophosphate (IMP) which can be converted to the nucleotides adenosine monophosphate(AMP) and guanosine monophosphate (GMP) nucleotides degradation involves the formation of the respective nucleotides (inosine , adenosine and guanosine) these are then metabolized to purines the Purina derived from IMP is hypxanthine which is converted by the enzyme xanthine oxidase first to xanthine and then to uric acid guanine can be metabolized to xanthine then to uric acid directly but adenine can not. However AMP can be converted to IMP by the enzyme AMP a deaminase and at the nucleoside level, adenosine can converted to inosine thus surphus GMP and AMP can be converted to uric acid and excreted. (Marshall, *et al*., 2004).

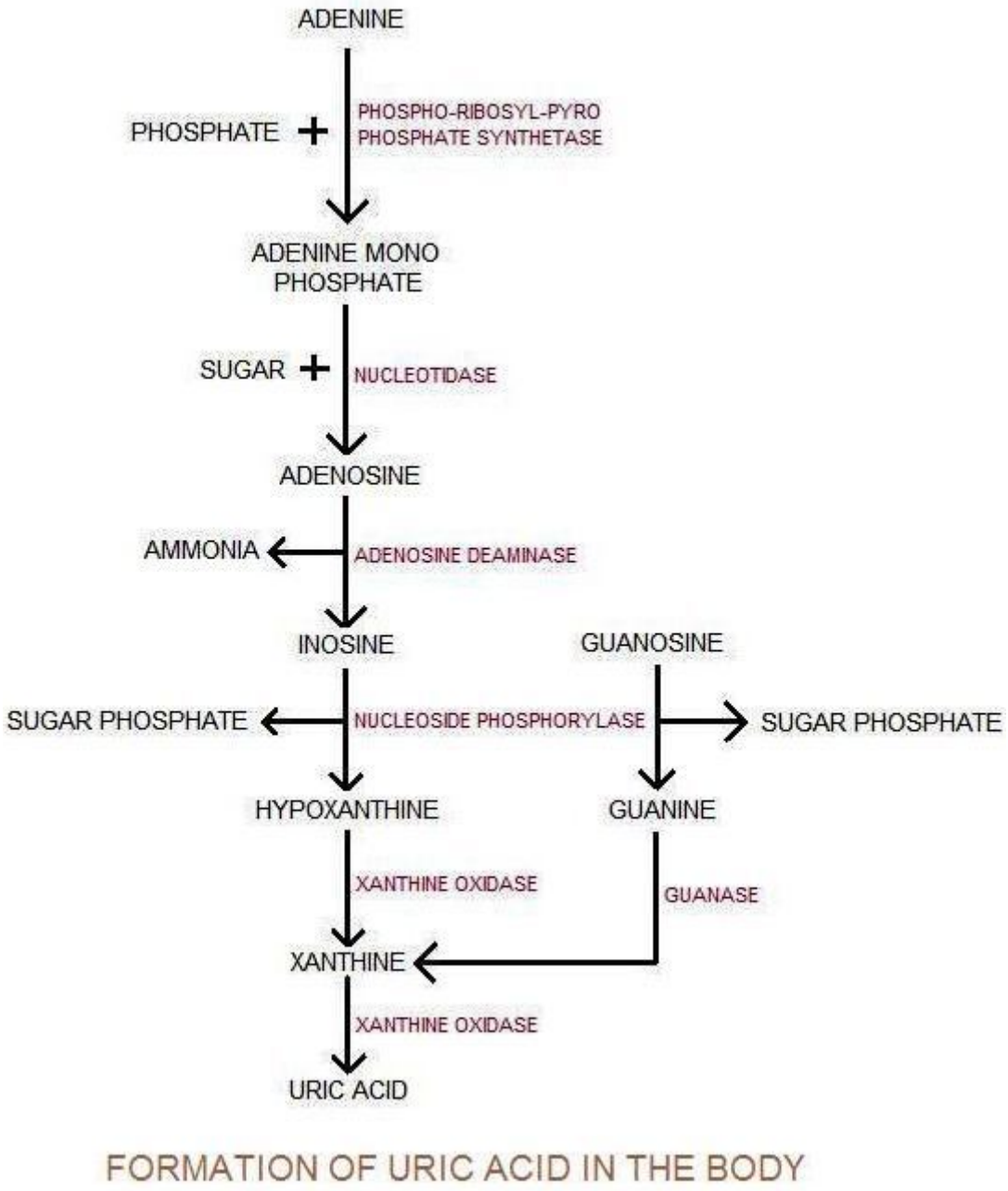

Figure (1.4): uric acid formation in the body.

♣Clinical Significance of uric acid:

1- Hyperuricemia:

Is most commonly defined by serum or plasma uric acid concentrations more than 7mg /dl in men or more than 6mg/dl in women (if the specific methods are used to measure uric acid) the major causes of hyperuricemia are sumarzed below:

Over production (associated with hyperuric arciduria ,underexcretion (associated with normal or decreased renal excretion of uric acid ,renal retention ,renal failure ,drud therapy :diuretic ,salicylates ,pyrazinamide,thambutol ,poisons : lead,alcohol,organic aciduria : acetoactate ,lactate ,endocrinopathies : hypothyroidism , hyperparathyroidism increased turnover of nucleic acid ,myeloproliferative syndromes chemotherapy of malignant tumors ,especially leukemia and lymphoma ,specific enzyme defects,deficiency of hypoxanthine ,guanine phosphoribosyl transferase complete (lesch _nyhan syndrome) ,partial abnormal phosphoribosyl pyrophosphate synthetase.

Asymptomatic hyperuricemia is frequently detected through biochemical screening

Long _term follow up of asymptomatic hyperuricemic subject is under taken because many are at risk for renal disease that may develop as a result of hyperuricemia and hyperuricosuria.(Tietz,1987).

Sudden increase in urate production, typically seen as a consequence of treatment of hematological malignancy can lead to widespread crystallization in the renal tubules causing obstruction and acute renal failure (acute urate nephropathy). (Marshall, *et al*., 2004).

2-Hypouricemia:

often defined as serum urate concentrations below 2 mg \ dl is much less common than hyperuricemia, it may be secondary to any one of a number of underlying conditions, sever hepatocellular disease with reduced purine synthesis or xanthine oxidase activity is one possibility, another is defective renal tubular reabsorption of uric acid either congenital as in general fanconis syndrome or acquired. (Tietz,1987).

uric acid is the primary waste product of purine metabolism ,the purines adenine and guanine are precursors of nucleic acid ATP and guanosine triphosphate (GTP) respectively ,uric acid has amolecular weight of 168 thus like creatinine it is readily filtered by the glomerulus but then it goes through acomplex cycle reabsorption and

secretion as it course through the nephron ,only 6% to 12 % from the original filtrate is finally excreted .uric acid exists in its ionized and more soluable form usually sodium urate at urinary pH values above5.75 (the first pKa of uric acid) at pH bleow 5.75 it is undissociated this fact has great clinical significane in the development of urolithasis (formation of calculi) and gout.(Bishop, *et al*., 2000).

1.2.5.2 Electrolytes:

Are ions capable of carrying an electric charge, they are classified as anions or cations based on the type of charge they carry. These names were determined years ago based on how the ion migrates in an electric field. Anions have a negative charge and move to ward the anode, whereas cations migrate in the direction of the cathode because of their positive charge. (Bishop, *et al*., 2000).

1.2.5.2.1Calcium:

Calcium is the most important mineral in the human body. The average of adult body contains approximately 25,000mmol of which 99% is bound in the skeleton, the total calcium content of the extra cellular fluid is only 22.5mmol of which 9mmol in the plasma .Most of the calcium in the bone is stable but approximately 500mmol \24h move between bone and extra cellular fluid to support calcium haemostasis in the kidneys, ionized calcium is filtered by the glomeruli (240mmol/24h) most of this is reabsorped in the tubules and normal renal calcium excretion is 2.5-7.5 mmol\24h because of the feacal loss, the minimum dietary requirement is about 12.5mmol\24h.(Mayn,1994).

Total body calcium:

The total body calcium depends on that absorbed from the dietary intake and that lost from the body. (Mayn, 1994).

♣Factors affecting intake:

About 25mmol (1g) of calcium is ingested per day , of which there is a net absorption of between 6 and 12 mmol (0.25_0.50) g .the active metabolite of vitamin D

1,25_dihydroxy vitamin D (1,25_dihydroxycholecalciferol) , is needed for adequate calcium absorption. (Mayn, 1994).

♣Factors affecting loss:

Calcium is lost in faeces and urine.

Faecal calcium is derived from the diet and that portion of the large amount of intestinal secretions that has not been reabsorbed and is therefore lost from the body. (Mayn,1994).

Calcium in the intestine, whether endogenous or exogenous in origin, may form insoluble, poorly absorbed complexes with phosphate or fatty acids. Orally administered phosphate may be used therapeutically to reduce calcium absorption and reabsorption. An excess of fatty acids in the intestinal lumen in steatorrhoea may contribute to calcium malabsorption. (Mayn, 1994).

Urinary calcium excretion depends on the amount of calcium reaching the glomeruli the glomerular filtration rate and on renal tubular function. Parathyroid hormone and 1, 25_dihydroxyvitamin D increase calcium and to a lesser extent urinary phosphate reabsorption. (Mayn, 1994).

Plasma calcium:

The mean plasma calcium concentration in healthy subjects is about 2.50mmol|L

(10 mg/dl). Calcium is present in plasma in three main forms:

- **That bound to proteins**, mainly albumin this accounts for a little less than half the total calcium concentration as measured by routine analytical methods. It is a physiologically inactive transport form, comparable with iron bound to transferring. (Mayn, 1994).
- **Free –ionized calcium** (Ca^{+2}) which comprises most of the rest. It is physiologically active fraction, comparable with free thyroxin. (Mayn,1994).
- **Complex to citrate and phosphate.**

♣Control of plasma calcium:

1. Diet and absorption:

Normal diet contains about 25 mmol of calcium, about 7 mmol secreted in gastrointestinal tract , about 12 mmol absorbed in duodenum and jejunum normal absorption requires adequate amounts of active vitamin D and excess of fatty acids , phosphate reduce absorption of calcium. (Mayn, 1994).

2. Renal excretion:

The normal filtered of calcium is depend on the level of ionized calcium and the glomerular filtration rate and is about 250 mmol|day, normal about 99% of the filtered calcium is reabsorb in proximal tubule giving the normal range of calcium in urine 2.5_7.5 mmol/day. Renal tubular reabsorption of calcium reduced by calcitonin but increased by parathyroid hormone. (Mayn,1994).

3. Bone as reservoir:

The body skeleton provides an enormous reservoir of calcium and phosphate which may be used either to supply or store calcium ions. The calcium bound with albumin in plasma to facilitate transport or exchange it between the ECF and bone crystals, which move in bone though the bone fluid, break down and synthesis in the adult are normally in balance. The mineral balance will be dependent on relative numbers and activities of osteoclast and osteoblast cell. Osteoclastic domination leads to anet break of bone and osteoblastic domination results in anet synthesis of bone increasing levels of parathyroid hormone and vitamin D increase the rate of break down. (Mayn,1994).

Calcium regulating hormones:

Calcium concentration in the extra cellular fluid is normally maintained within narrow limit by a control system involving two hormones: Parathyroid hormone and 1,25dihydroxycholecaciferol these hormones also control the inorganic phosphate concentration of the extra cellular. Calcitonin probably has only a minor role in calcium haemostatic. (Mayn,1994).

♣Disorders of calcium metabolism:

1-Hypercalcemia:

Hypercalcaemia with hypophosphatemia relative to GFR:

True free-ionized hypercalcemia with hypophosphatemia is caused by inappropriate secretion of PTH or PTHRP.the term inappropriate indicate that the release of hormone into circulation is not adequately inhibited by negative feedback control. Inappropriate PTH secretion occurs in the following clinical situations. (Mayn,1994).

PTH production by the parathyroid glands due to:

Primary hyperparathyroidism

Tertiary hyperparathyroidism

PTHRP production by non-parathyroid tissue.

If renal glomerular function is adequate the high circulating PTH or PTHRP concentrations cause hypercalcemia , which is associated with a low normal or low plasma phosphate concentration in relation to GFR and to phosphaturia. If the glomerular damage develops due to hypercalcemia, the kidneys cannot respond normally to the phosphaturic effect of PTH and because of impaired hydroxylation of 25-OHD_3, plasma calcium concentrations may fall towards or within normal range as renal failure progresses. Because plasma phosphate concentrations tend to rise. (Mayn,1994).

Hypercalcemia with hyperphosphatemia relative to the GFR:

May be due to:

1- Vitamin D excess.

2- Sarcoidosis.

3-sever hyperthyroidism.

2-Hypocalcemia:

May cause by:

1- Reduced intake and absorption of calcium and vitamin D.

2- Impaired metabolism of vitamin D.

3-sugical causes eg; hypoparathyroidism is the most commonly caused by surgical damage to the parathyroid glands. (Mayn,1994).

1.2.5.2.3 Phosphate:

♣Physiology:

Found every where in living cells, phosphate compounds participate in many of the most important biochemical processes. The genetic materials deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are complex phosphodiesters. Most coenzyme are esters of phosphoric or pyrophosphoric acid. (Mayn,1994).

The most coenzymes are esters of phosphoric or pyrophosphoric acid. The most important reservoirs of biochemical energy are ATP, creatinine phosphate, and phosphoenolpyruvate. Phosphate deficiency can lead to ATP depletion, which is ultimately responsible for many of the clinical symptoms observed in hypophosphatemia.

Alterations in the concentration of 2,3-biphosphoglycerate(2,3-BPG) in red blood cells affect the affinity of hemoglobin for oxygen, with an increase facilitating the release of oxygen in tissue and a decrease making oxygen bound to hemoglobin less available. By affecting the formation of 2, 3-BPG, the concentration of in organic phosphate indirectly affects the release of oxygen from hemoglobin. (Mayn,1994).

Understanding the cause of an altered phosphate concentration in the blood is often difficult because transcellular shifts of phosphate are a major cause of hypophosphatemia in blood. That is, an in increased shift of phosphate into cells can deplete phosphate in the blood. Once phosphate is taken up by the cell, it remains there to be used in the synthesis of phosphorelated compounds. As these phosphate compounds are metabolized, inorganic phosphate slowly leaks out of the cell into the blood, where it is regulated principally by the kidney. The total body phosphorus is around 700 grams (23,000mmol) and is distributed mainly in bones (80%), viscera (10.9%), skeletal muscles (9%) and only 0.1% is the is extra cellular space. (Mayn,1994).

The average diet usually provides 800-1400 mg of phosphorous daily of which 60-80% is absorbed in the gut mainly by passive transport and there is also active transport of phosphorous via the action of 1,25dihydroxy vitamin D_3.

Parathyroid hormone and low phosphorus diet also stimulate absorption of phosphorus. The normal level (expressed as phosphate) is usually between (0.84-1.44mmol\L or (2.8-4.5 mg\dl) the plasma concentration of phosphorous is determined by dietary intake intestinal absorption, renal tubular reabsorption and transfer between intra and extra cellular fluid compartments. (Mayn,1994).

Kidneys remain the most important regulator of serum phosphorus absorbed from intestines and the amount excreted in the urine, phosphate is freely filtered across the glomerulus of which 80% is reabsorbed in the proximal tubules and small amount in the distal tubules. (Mayn,1994).

♣Clinical application:

1- Hypophosphatemia:

Occur in about 1% to 5% of phosphatized patients. The increase of hypophosphatemia increase to 20% to 40% in patients with the following disorders: diabetic ketoacidosis, chronic obstructive pulmonary disease (COPD), asthma, malignancy, long term treatment

with total parental nutrition (TPN). Inflammatory bowel disease, anorexia nervosa, and alcoholism. The incidence increases to 60% to 80% in ICU patients with sepsis. In addition, hypophosphatemia can also be caused by increased renal excretion, as with hyperparathyroidism, and decreased intestinal absorption as with vitamin D deficiency or antacid use. hypophosphate, associated with disturbances of calcium metabolism is usually due to high circulating PTH concentrations in such conditions, and in renal tubular disorders of phosphate reabsorption.phosphate is lost from the body in urine.hypophosphatemia may also be caused by severe and prolonged dietary deficiency; urinary phosphate excretion is then usually significantly reduced. (Mayn,1994).

Phosphate, like potassium, enters cells from the extracelluar fluid if the rate of glucose metabolism is increased. This may be associated with glucose infusion during for example, the treatment of diabetic coma with insulin. The redistribution of phosphate is a common cause of hypophosphatemia in patients receiving parental nutrition with insulin and glucose. Long-term parenteral feeding without phosphate supplementation may cause true phosphate depletion. Hypophosphataemia in such circumstances, whether due to deficiency or redistribution, may cause neurological abnormalities such as convulsions. (Mayn,1994).

2- Hyperphosphatemia:

Patients at greatest risk for hyperpphosphatemia are those with acute or chronic renal failure. An increased intake of phosphate or increased released of cellular phosphate may also cause hyperphosphatemia. Because they may not yet have developed mature PTH and vitamin D metabolism, neonates are especially susceptible to hyperphosphatemia caused by increased intake, such as from cow milk. Increased breakdown of cells can some times lead to hyperphosphatemia, as with sever infections, intensive exercise neoplastic disorders, or intracellular hemolysis. Because immature lymphoblast have leukemia are especially susceptible to hyperphosphataemia. (Mayn,1994).

Normal plasma phosphate concentrations are higher in infants and children than in adults. The commonest cause of hyperphosphataemia is renal glomerular dysfunction; it is important not to correct hypocalcaemia until this abnormality has been corrected. Less common causes include hypoparathyroidism and acromegaly. (Mayn, 1994).

♣Hemodialysis: (artificial kidney)

Is the replacement of certain elements from the blood by use of the difference in the rates of either diffusion through a semipermable membrane .It is used to remove toxic substance from the blood when the kidney are not able to remove them satisfactorily from the circulation.(Norbert, 2001)

Severe loss of kidney function either acutely or chronically, is a threat to life, requires removal of toxic waste products and restoration of body fluid volume and composition toward normal. This can be accomplished by dialysis with an artificial kidney. In certain types of acute renal failure an artificial kidneys may be used to tide the patient over until the kidneys resume their function if the loss of function irreversible, it is necessary to perform dialysis chronically to maintain life. (Norbert, 2001)

Thousands of people with irreversible renal failure or even total kidney removed are being maintained for 15 to 20 years by dialysis with artificial kidneys because dialysis with artificial kidney can not maintain completely normal body fluid composition and can not replace all multiple functions performed by the kidney, the health of patients maintained on artificial kidneys usually remains significantly impaired. A better treatment for permanent loss of kidney function is to restore functional kidney tissue by means of kidney transplant. (Norbert, 2001).

♣Basic principle of dialysis:

The basic principle of the artificial kidney is to pass blood through minute blood channels bounded by a thin membrane. On other side of the membrane is a dialyzing fluid into which unwanted substances in the blood pass by diffusion. (Arthur, 2000).

Figure (1.5) shows the components of one type of artificial kidney in which blood flows continually between two thin membrane of cellophane, out side the membrane is dialyzing fluid, the cellophane is porous enough to allow the constituents of the plasma, except the plasma proteins to diffuse in both directions from plasma into the dialyzing fluid or from the dialyzing fluid back into the plasma if the concentration of a substance

is greater in the plasma than in the dialyzing fluid there will be net transfer of the substance from the plasma into dialyzing fluid. (Arthur,2000).

The rate of movement of solute across the dialyzing membrane depends on:

(a) Concentration gradient of the solute between the two solutions.

(b) The permeability of the membrane to the solute.

(c) The surface area of the membrane.

(d) The length of time that the blood and fluid remain in contact with the membrane.

Thus the maximum rate of the solute transfer occurs initially when the concentration gradient is greatest (when dialysis is begun) and slows down as the concentration gradient is dissipated. In a flowing system as is the case with hemodialysis.

In which blood and dialysate fluid flow through the artificial kidney the dissipation of the concentration gradient can be reduced and diffusion of solute across the membrane can be optimized by increasing the flow rate of either or both the blood and the dialyzing fluid. (Arthur, 2000).

In normal operation of the artificial kidney, blood flows continually or intermittently back into the vein. The total amount of blood in artificial kidney at many one time is usually less than 500 milliliters; the rate of flow may be several hundred milliliters per minute and the total diffusion surface area between 0.6_2.5 square meters. To prevent coagulation of the blood in fused into the blood as it enters the artificial kidney. (Arthur, 2000).

In addition to diffusion of solutes mass transfer of solutes and water can be produced by Appling hydrostatic pressure to force the fluid and solutes by the process of filtration across the membranes of the dialyzer, such filtration is called bulk flow. (Arthur, 2000).

♣Dialyzing Fluid:

Note that the concentrations of ions and other substances in normal plasma or uremic plasma. Instead, they are adjusted to levels that are needed to cause appropriate movement of water and solutes through the membrane during the dialysis.

Note that there is no phosphate, urea, urate, sulfate or creatinine in the dialyzing fluid, how ever these are present in high concentration in the uremic blood.

There fore when the uremic patient is dialyzed, these substances are lost in large quantities into the dialyzing fluid. (Arthur, 2000).

♣Types of hemodialysis:

There are three types of hemodialysis: conventional hemodialysis, daily hemodialysis, and nocturnal hemodialysis. Below is the adaption and summary from a brochure of The Ottawa Hospital. (Arthur, 2000).

a. Conventional hemodialysis:

Chronic hemodialysis is usually done three times per week, for about 3–4 hours for each treatment, during which the patient's blood is drawn out through a tube at a rate of 200-400 mL/min. The tube is connected to a 15, 16, or 17 gauge needle inserted in the dialysis fistula or graft, or connected to one port of a dialysis catheter. The blood is then pumped through the dialyzer, and then the processed blood is pumped back into the patient's bloodstream through another tube (connected to a second needle or port). During the procedure, the patient's blood pressure is closely monitored, and if it becomes low, or the patient develops any other signs of low blood volume such as nausea, the dialysis attendant can administer extra fluid through the machine. During the treatment, the patient's entire blood volume (about 5000 cc) circulates through the machine every 15 minutes. During this process, the dialysis patient is exposed to a week's worth of water for the average person. (Arthur, 2000).

B. Daily hemodialysis:

Daily hemodialysis is typically used by those patients who do their own dialysis at home. It is less stressful (more gentle) but does require more frequent access. This is simple with catheters, but more problematic with fistulas or grafts. The "buttonhole technique" can be used for fistulas requiring frequent access. Daily hemodialysis is usually done for 2 hours six days a week. (Arthur, 2000).

C. Nocturnal hemodialysis:

The procedure of nocturnal hemodialysis is similar to conventional hemodialysis except it is performed three to six nights a week and between six and ten hours per session while the patient sleeps. (Arthur, 2000).

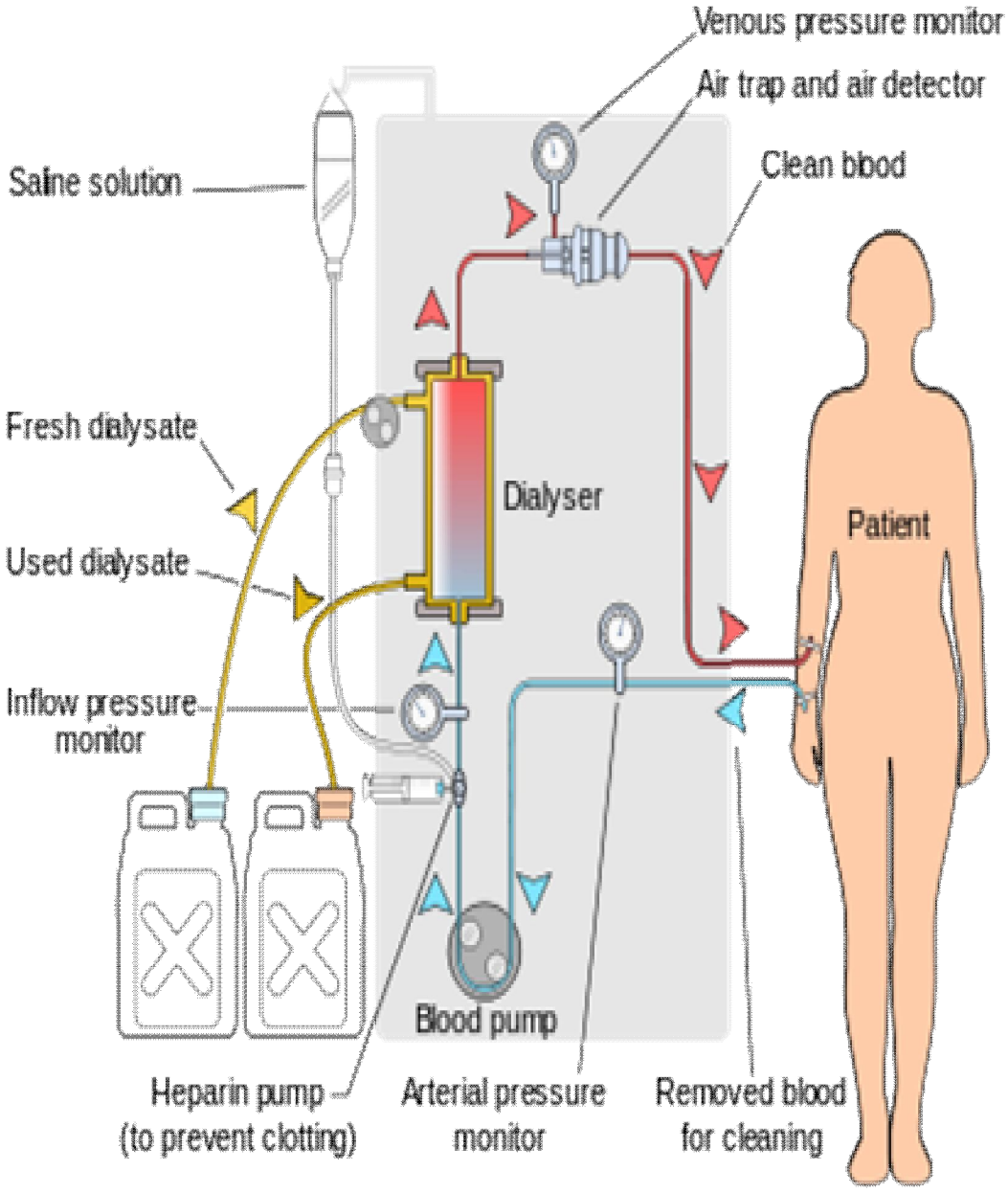

Figure (1.5): Show components of one type of artificial kidney

The hemodialysis machine pumps the patient's blood and the dialysate through the dialyzer. The newest dialysis machines on the market are highly computerized and continuously monitor an array of safety-critical parameters, including blood and dialysate flow rates; dialysis solution conductivity, temperature, and pH; and analysis of the dialysate for evidence of blood leakage or presence of air. Any reading that is out of normal range triggers an audible alarm to alert the patient-care technician who is monitoring the patient. Manufacturers of dialysis machines include companies such as Nipro,Fresenius, Gambro, Baxter, B. Braun, NxStage and Bellco. (Arthur, 2000).

- **Dialyzer**:

The dialyzer is the piece of equipment that actually filters the blood. Almost all dialyzers in use today are of the hollow-fiber variety. A cylindrical bundle of hollow fibers, whose walls are composed of semi-permeable membrane, is anchored at each end into potting compound (a sort of glue). This assembly is then put into a clear plastic cylindrical shell with four openings. One opening or blood port at each end of the cylinder communicates with each end of the bundle of hollow fibers. This forms the "blood compartment" of the dialyzer. Two other ports are cut into the side of the cylinder. These communicate with the space around the hollow fibers, the "dialysate compartment." Blood is pumped via the blood ports through this bundle of very thin capillary-like tubes, and the dialysate is pumped through the space surrounding the fibers. Pressure gradients are applied when necessary to move fluid from the blood to the dialysate compartment. (Arthur, 2000).

1.3 Association of uric acid, calcium and phosphate with chronic renal failure:

1.3.1 Uric acid:

Chronic renal disease causes increased uric acid concentration because filtration and secretion are impaired. How ever, uric acid is not useful as indicator of renal function because many other factors affect its plasma concentration. Accumulations of uric acid lead to toxicity. (Fieg, 2008).

1.3.2phosphate and calcium:

As glomerular filtration rate (GFR) declines, there is a decreased in phosphate excretion resulting in phosphate retention, while serum calcium decrease and production of calcitriol is suppressed. (Malluche, 2004).

These metabolic changes cause the stimulation of parathyroid hormone production as adaptive response to maintain normal serum phosphate and calcium concentrations. (Levin, 2005).

Reduced calcitriol levels lead to impaired gastrointestinal calcium absorption, there by leading to hypocalcaemia hyperphosphatemia, hypocalcaemia and reduced calcitriol synthesis all promote the production of parathyroid hormone and proliferation of parathyroid cells resulting in secondary hyperparathyroidism. (Slatopolsky, 1999).

Phosphate binding agents are indicating for treating elevated phosphorus levels in the vast majority of patients undergoing hemodialysis. (Bleyer, 2003).

Hyperparathyroidism to compensate for hypocalcaemia caused either by hyperphosphatemia (po^{-}_{4} binds and lower ionized ca^{+2}) or altered vit D metabolism. (Bushinky, 1998).

Patients at risk for hyperphosphatemia are those with acute or chronic renal failure. (Shiber, 2002).

1.4 Objectives:

1.4.1 General objectives:

To measure serum uric acid, phosphate and calcium of patatients with chronic renal failure pre and post hemodialysis.

1.4.2 Specific Objectives:

To correlate between duration of disease and level of serum uric acid, calcium and phosphate before dialysis.