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Some Aspects In The Physiological Changes In Patients With Renal Failure

A Thesis

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for the Degree of Master of Sciences in Medical Physiology*

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بعض جوانب التغيرات الفسلجية للمرضى المصابين بالفشل الكلوي

رسالة

مقدمة إلى مجلس كلية الطب في جامعة بابل كجزء من متطلبات الحصول على درجة

الماجستير في علم الفسلجة الطبية

من قبل

أسيل كامل شاكر

بكالوريوس طب و جراحة عامة

بإشراف

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دكتوراه في علم الفسلجة

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
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صدق الله العلي العظيم

سورة الإسراء

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الخلاصة

الفشل الكلوي المزمن هو متلازمة مرضية تحدث نتيجة تلف تقدمي في التركيب الكلوي بواسطة مسببات مرضية كلوية تعمل على إعاقة الوظائف الكلوية بصورة تدريجية. قد يحدث العجز الكلوي المزمن نتيجة لعدد من الحالات التي تسبب فقدان دائم للنبيبات الكلوية ومن هذه الحالات التهاب حوض الكلى المزمن , التهاب الكبيبات الكلوية المرافق للسكري أو غير المرافق له, تصلب النبيبات الكلوية المرافق لارتفاع ضغط الدم , انسداد المجاري البولية , مرض تعدد الأكياس الكلوي والأدوية والسموم . بغض النظر عن السبب فان الفشل الكلوي المزمن يسبب فقدان الخلايا الكلوية وإعاقة الترشيح الكلوي وتقليل قابلية الأنابيب الكلوية على إعادة الامتصاص وتؤثر على وظائف الغدد الصم للكلية.

الهدف من هذه الدراسة هو تقييم بعض جوانب التغيرات الفسلجية الكيميائية الحياتية والدموية للمرضى المصابين بالفشل الكلوي المزمن الخاضعين للديليزة الدموية.

تمت الدراسة في وحدة الكلية الصناعية في مستشفى مرجان التعليمي في مدينه بابل. ثلاثة وستون مريضاً مع ثلاثة وستين من الأصحاء تطوعوا للاشتراك في الدراسة. تم تقسيم كلاً من المرضى و الأصحاء إلى ستة مجاميع عمرية وتم اخذ عينات الدم منهم لغرض قياس بعض التحاليل الكيميائية الحياتية والدموية وتم مقارنه نتائج هذه العينات بين المرضى والأصحاء .

أظهرت الدراسة إن هناك زيادة بفرق معنوي ملحوظ في بعض المقاييس للمرضى من الذكور والإناث, وهذه المقاييس هي اليوريا, الكرياتينين, حامض اليوريك, فحص وظائف الكبد , الترايكلسرايد , HDL و مستويات البوتاسيوم والفسفور.

أظهرت الدراسة إن هناك نقصان بفرق معنوي ملحوظ في بعض المقاييس للمرضى من الذكور والإناث, وهذه المقاييس هي بروتينات مصل الدم, الألبومين , الكوليوليون , LDL, vLDL , ومستويات النحاس والزنك .

كذلك أظهرت الدراسة عدم وجود فرق معنوي ملحوظ في بعض المقاييس للمرضى من الذكور والإناث, وهذه المقاييس هي سكر الدم, البلروبين غير المباشر و مستويات الكالسيوم والصوديوم .

تدعم دراستنا الفرضية المعروفة بأن الفشل الكلوي المزمن هو مرض خطير يسبب تأثيرا كبيرا على عدة أجهزة في الجسم لذلك فأن المرضى المعرضين للإصابة بهذا المرض يجب أن يتم تشخيصهم ومعالجتهم مبكرا . إن التأخير في تشخيص وعلاج الفشل الكلوي المزمن وعدم القدرة على تشخيص علاماته الأولى يبقى أمرا يدعو للاهتمام في بلدنا . إن تقيس تصفية الكرياتينين ومعدل تصفية النبيتات الكلوية يجب أن تعمل لكل المرضى المعرضين للإصابة بهذا المرض. إن الأمراض الكلوية يجب أن تعامل بجدية ويتم التعامل معها بجدية ضمن برامجيات الخدمات الصحية في عيادات تخصصية مجهزة بأحدث التقنيات بالإضافة إلى تحليل معطيات المرضى بدقة. إن نسبة فقر الدم وارتفاع ضغط الدم في هذه الدراسة كان عاليا جدا لذلك فأن مثل هذه النسب تستدعي اهتماما جيدا لدراسة مختلف مشاكل المرضى وإيجاد الحلول لها .

CERTIFICATE

We certify that this thesis, titled **(Some aspects in the physiological changes in patients with renal failure)** was prepared under our supervision at the department of medical physiology, college of Medicine, university of Babylon as a partial fulfillment of the requirements for the degree of Master of Science in medical physiology .

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Introduction

Renal failure is a condition in which the kidneys fail to remove and concentrate metabolic end products from the blood, regulate the fluid, electrolytes, and pH balance of the extracellular fluids. The underlying cause may be renal disease, systemic disease, and/or urologic defects of non renal origin **(Kasper et al.,2005)**. Renal failure can occur as an acute or a chronic disorder. **(Robert et al.,2006;Nitescu.,2007)**.

Acute renal failure represents a rapid decline in renal function sufficient to increase blood levels of nitrogenous wastes and impair fluid and electrolyte balance **(Robert &Albright.,2001)**.Acute renal failure is potentially reversible if the precipitating factors can be corrected before permanent kidney damage(**Singri et al.,2003**). The most common indicator of acute renal failure is azotemia, an accumulation of nitrogenous wastes in the blood **(Hilton.,2006)** .

On the other hand, chronic renal failure (CRF) represents progressive and irreversible destruction of kidneys structures **(Kasaka et al.,2004)**. Many patients with chronic renal failure progressed to the final stages of the disease and then died. It seems that (CRF) is the major cause of death from renal diseases . CRF can result from a number of conditions that cause permanent loss of nephrons, including chronic pyelonephritis ,diabetic and non diabetic glomerulonephritis, hypertensive nephrosclerosis, obstructive uropathies ,polycystic kidneys , drugs and toxins **(Bethesda., 2007)**.

Diabetic kidney diseases are the largest single cause of kidney failure in the word **(Porth.,2007)**.

Chapter One. Introduction

Chronic renal failure results in loss of renal cells with progressive deterioration of glomerular filtration, tubular reabsorptive capacity, and endocrine functions of the kidneys. **(Yu., 2003)**. All forms of renal failure are characterized by a reduction in the GFR, reflecting a corresponding reduction in the number of functional nephron. The rate of nephron destruction differs from case to case, ranging from several months to many years **(Levey et al .,2003)**.

The manifestations of chronic renal failure include an accumulation of nitrogenous wastes, alterations in water, electrolytes, and acid-base balance, mineral and skeletal disorders, anemia and coagulation disorders, hypertension and alterations in cardiovascular function, gastrointestinal disorders, neurologic complications, disorders of skin integrity, and immunologic disorders **(Albaaj & Hutchison.,2003)**.

The manifestations of renal failure are determined largely by the extent of renal function that is present, coexisting disease conditions, and the type of renal replacement therapy that the person is receiving. The progression of chronic renal failure usually occurs in four stages: diminished renal reserve, renal insufficiency, renal failure, and End-stage renal disease (ESRD) **(Cotran et al., 1999)**. Renal insufficiency represents a reduction in the GFR to approximately 20% - 50% of normal; renal failure, a reduction to less than 20% - 25% of normal; and ESRD, a decrease in GFR to less than 5% of normal **(Levey et al.,2005)**.

End-stage renal disease almost affects every body system. It causes an accumulation of nitrogenous wastes (i.e., azotemia), alters sodium and water excretion, a alters regulation of body levels of electrolytes (potassium, phosphate, calcium, and magnesium). It also causes skeletal disorders(bones and muscles), anemia, alterations in cardiovascular functions, neurologic disturbances, gastrointestinal

Chapter One. Introduction

dysfunction, and discomforting skin changes(like pruritis) **(Levey et al.,2003)**.

The treatment of ESRD can be divided into two types: conservative management of renal insufficiency and renal replacement therapy with dialysis and/or transplantation **(Stevens et al.,2006)**. Conservative treatment consists of measures to prevent or retard deterioration in remaining renal functions and to assist the body in compensating for the existing impairment. **(Pamar.,2002)** Interventions that have been shown to retard significantly the progression of chronic renal insufficiency include dietary protein restriction and blood pressure normalization. In addition activated vitamin D can be used to increase calcium absorption and control secondary hyperparathyroidism **(Karalliedde et al.,2008)**. Recombinant human erythropoietin is used to treat the profound anemia that occurs in persons with ESRD**(Tong & Nissenson .,2001)**.

This study aimed to estimate some hematological and biochemical parameters in patients suffering from CRF in the artificial renal unite on continuous hemodialysis . The levels of these hematological and biochemical parameters are very important to estimate the patient condition, prognosis of the disease and prediction of its complications in order to prevent and treat these disorders .It also helps the health care staff in the unite to know how the body is responding to the different therapies that being provided to these seriously ill patients.

Review Of Literature

Anatomy and histology of renal system

2-1- Renal System

The urinary system and the kidneys retains useful materials and excrete foreign or excessive materials and waste. Through this basic function, the kidneys profoundly affect other body systems and the person's overall health (**Ganong., 2005**).The urinary system consists of two kidneys, two ureters, one bladder and one urethra. (**Andreoli et al., 2004**).

2-1-1-The kidneys

The kidneys are bean-shaped highly vascular organs that measure approximately 4 ½" long and 2 ½" wide in the normal adult male. Located retroperitoneally .They lie on either side of the vertebral column, between the 12th thoracic and the 3rd lumbar vertebrae (**Seeley et al .,1995**). Crowded by the liver, the right kidney extends slightly lower than the left. At the top of each kidney lies an adrenal gland. At the hilus , an indentation in the kidney's medial aspect , the renal artery, renal vein, lymphatic vessels, and nerves enter the kidney. The renal pelvis, a funnel shaped ureter extension, also enters here (**Solomon et al.,1990**).

2-1-2-The ureters

The ureters act as ducts to allow urine to pass from the kidneys to the bladder. They measure about 25 to 30 cm long in adults and have a diameter varying from 2 to 8 mm (**Romanes .,1996**). Ureters channel urine via peristaltic waves to the bladder one to five times per minute (**Zanoschi.,2005**).

2-1-3-The nephron

The nephron is the basic, functional unit of the kidney. They perform two main activities, mechanical filtration of fluids, wastes, electrolytes, acids and bases into the tubular system; and selective reabsorption and secretion of ions (**Moore & Agur.,2002**). Three processes : glomerular filtration, tubular reabsorption, and tubular secretion take place in the nephrons, ultimately leading to urine formation (**Ganong.,2005**). The kidneys can vary the amount of substances reabsorbed and secreted in the nephrons, changing the composition of urine excreted. Daily urine output averages 720 to 2,400 ml. (**Bennett&Plum.,1996**). The GFR is considered the best measure of overall function of the kidney. The normal level of GFR varies with age, sex, and body size. The normal GFR for young healthy adults is approximately 120 to 130 ml /min (1.73 ml/min per m²) (**Levey et al.,2003**).

2-1-4-The bladder

The bladder is a hollow, spherical, muscular organ in the pelvis that serves to store urine. It lies anterior and inferior to the pelvic cavity and posterior to the symphysis pubis. Bladder capacity ranges from 500 to 600 ml in a normal adult (**Moore&Agure.,2002**). The base of the bladder contains three openings that form a triangular area called the trigone. Two ureteral orifices and one urethral orifice (**Romanes.,1996**). Urination results from involuntary reflex (Parasympathetic stimulation)and voluntary processes(central nervous stimulation) (**Ganong.,2005**).

2-1-5-The urethra

The urethra is a small duct that channels urine outside the body from the bladder. It has an exterior opening (urethral meatus) . In the female, the urethra ranges from 2.5 to 5 cm long. In the male, the urethra is approximately 20 cm. long (**Bennett&Plum.,1996**).

2-2-Renal Failure

Renal failure is a condition in which the kidneys fail to remove metabolic end products from the blood and regulate the fluid, electrolyte, and pH balance of the extracellular fluids. The underlying cause may be renal disease, systemic disease, or urologic defects of non renal origin. Renal failure can occur as an acute or a chronic disorder (**Kasper et al.,2005**).

2-2-1 Acute Renal Failure

Acute renal failure (ARF) is the sudden interruption of kidney function from obstruction, reduced circulation, or disease in the kidney tissue. usually reversible with treatment. Otherwise, it can progress to end-stage renal disease(ESRD) or chronic renal failure (**Ferrone .,2003; Nitescu.,2007**) . However, an increased serum creatinine, accumulation of other nitrogenous-based waste s, and a decline in urinary output are the hallmarks of ARF (**Albright.,2001; Ress &Shaw .,2007**).

ARF is potentially reversible if the precipitating factors can be corrected before permanent kidney damage has occurred. ARF is a common threat to patients in intensive care units, with a mortality rate ranging from 40% to 75% (**Thadhani et al.,1996; Albright. ,2001; Singri et al.,2003**). The mortality rate from acute renal failure has not changed substantially since the 1960s (**Molitoris et al.,2000**), this probably because ARF is seen more often in older persons than before, and it

frequently superimposed on other life-threatening conditions, such as trauma, shock, and sepsis .In ARF, the glomerular filtration rate (GFR) is decreased. As a result, excretion of nitrogenous wastes is reduced, and fluid and electrolyte balance cannot be maintained (**Hilton. ,2006**) .

The causes of ARF can be Pre-renal, post renal, and intrinsic renal (**Robert &Albright .,2001**) .Overall, 60% of cases of community-acquired ARF are due to Prerenal condition (**Liano & Pascual .,1996**).

2-2-1-1- Pre Renal Failure

The most common form of ARF, is associated with diminished blood flow to the kidneys . It is reversible if the cause of the decreased renal blood flow can be identified and corrected before kidney damage occurs (**Liano & Pascual .,1996**). Renal auto-regulation chiefly depends on a combination of pre-glomerular arteriolar vasodilatation, mediated by prostaglandins and nitric oxide, and post-glomerular arteriolar vasoconstriction, mediated by Angiotensin-II(**Hilton.,2006**). Non-steroidal anti inflammatory drugs or selective cyclo-oxygenase 2 inhibitors, and angiotensin converting enzyme inhibitors may provoke pre-renal acute renal failure in particular clinical settings (**Porth ., 2007 ; Agarwal et al.,2008**) .People at high risk include elderly patients with atherosclerotic cardiovascular disease (CVD), patients with pre-existing chronic kidney disease (CKD), and patients with renal hypoperfusion (**Bevan.,2000;Robert &Albright .,2001**).

2-2-1-2- Intrinsic Renal Failure

It results from conditions that cause damage to structures within the kidney ((**Bellomo et al. ,2004**). It may result from streptococcal infections, lupus, sickle cell disease, cancers, or nephrotoxins (**Abuelo ., 1995**).The major causes of intrinsic failure are ischemia associated with

prerenal failure. Acute tubular necrosis is most common and often is ischemic or toxic in origin (**Tepel et al.,2002**).

2-2-1-3- Post Renal Failure

It is caused by obstruction of urinary outflow by blood clots, renal calculi, tumors, prostate enlargement and strictures. The obstruction can occur in the ureter, bladder, or urethra. Prostatic hyperplasia is the most common underlying problem (**Chapman&Reid.,1991; Bhandari et al.,1995**).Because both ureters must be occluded to produce renal failure, obstruction of the bladder rarely causes ARF (**Snyder & Pendergraph.,2005**).The treatment consists of treating the underlying cause of obstruction (**Lameire et al.,2005**).

2-2-1- 4-Assessment Findings In Renal Failure

Patient may suffer from a little or no urine output, edema of the extremities, tachypnea as a result of the body attempts to compensate for worsening acidosis by blowing off excess CO₂ (**Dubose et al.,1991**),altered level of consciousness, pallor, hypotension and tachycardia(**Lameire et al.,2005**).In most instances, patients with CRF may exhibit some of the same symptoms ARF (**Kumer&Clark.,2006**).

2-2-2- Chronic Renal Failure

Chronic renal failure (CRF) is a pathological syndrome develops due to a progressive destruction of renal structures by chronic nephropathies. It is characterized by a gradually increasing renal function impairment. Most symptoms are due to metabolic disorders, caused by the accumulation of toxic substances in body fluids, which interfere with cellular processes (**Kasaka et al.,2004;Porth.,2007**) .

2-2-2-1-Stages of CRF Progression

CRF results in the loss of renal cells with a progressive deterioration of glomerular filtration, tubular re-absorptive capacity, and endocrine functions of the kidneys (Yu., 2003). All forms of renal failure are characterized by a reduction in the glomerular filtration rate GFR, reflecting a corresponding reduction in the number of functional nephrons. The rate of nephron destruction differs from case to case, ranging from several months to many years (Levey et al .,2003).CRF is categorized into five stages according to the (GFR) and the presence of signs of kidney damage and these are: **stage 1:**GFR is normal or > 90 ml/min , **stage 2:**GFR = 60-89 ml/min ,**stage3:** GFR = 30-59 ml/min, **stage 4:** GFR = 15-29 ml/min, and **stage 5:** GFR < 15 ml/min (National Kidney foundation., 2002;Levey et al.,2005).

On the other hand and according to Cotran et. al., classification, the progression of CRF may be classified into four stages: Silent (diminished renal reserve) – GFR up to 50 ml/min, Renal insufficiency – GFR 25 to 50 ml/min, Renal failure – GFR 5 to 25 ml/min, End-stage renal failure – GFR less than 5 ml/min(Cotran et al., 1999).

Uremia is a term applied to the manifestations of organ dysfunction seen in stages 3 and 4 (Levey et al.,2005). Azotemia means the accumulation of nitrogenous waste can be manifested in all stage of CRF, but it is still blood urea represent the hall mark of renal failure (Bennett&Plum.,1996;Meyer & Hostetter.,2007).The signs and symptoms of CRF occur gradually and do not become evident until the disease is far advanced. This is because of the amazing compensatory ability of the kidneys(Sarnak et al.,2005;Porth.,2007). As kidney structures are destroyed, the remaining nephrons undergo structural and functional hypertrophy (Fig. 2-1). It is only when the few remaining

nephrons are destroyed at that instance the manifestations of renal failure become evident (**Aunapuu et al.,2003;Vanholder et al., 2008**).

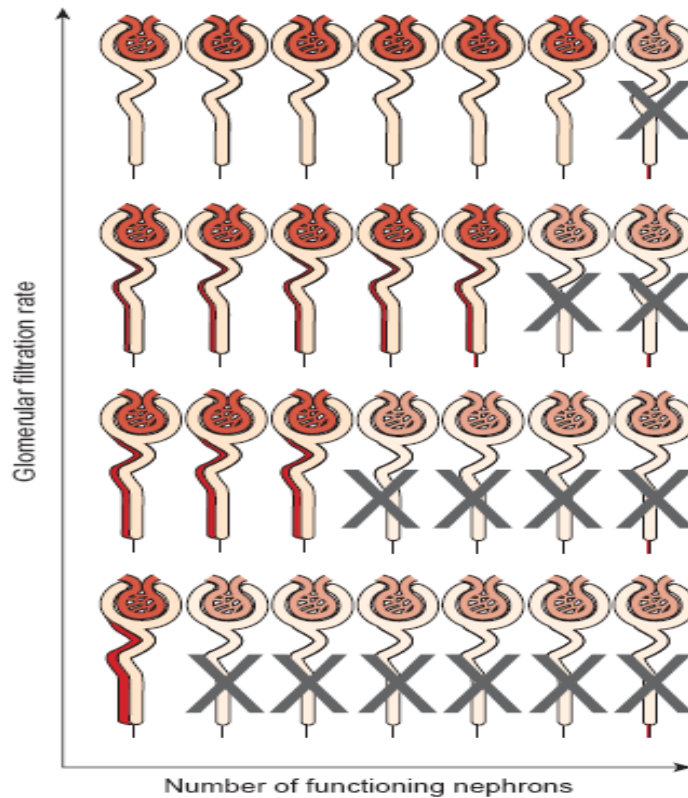


Figure 2-1: Relation of renal function and nephron mass. A proportional relation exists between the number of nephrons affected by disease and the resulting glomerular filtration rate (**Porth.,2007**).

2-2-2-1-1-Diminished Renal Reserve

Occurs when the GFR drops to approximately 50% of normal. At this point, the serum blood urea nitrogen (BUN) and creatinine levels are still normal, and no symptoms are evident (**Stevens et al.,2006**). This is supported by the fact that many persons survive an entire lifetime with only one kidney(**Ganong., 2005**). Because of the diminished reserve, the risk for development of azotemia increases with an additional renal insult,

such as that due to nephrotoxic drugs and chemotherapeutic agent (Kleber *et al.*,2007;Dale &Federman.,2003).

2-2-2-1-2-Renal Insufficiency

Occurs when the GFR decline to 20% to 50% of the normal. As nephrons are destroyed, the remaining nephrons undergo changes to compensate for those that are lost (Aunapuu *et al.*,2003). Each of the remaining nephrons must filter more solute particles from the blood. The solute particles are osmotically active, they cause more water to be lost in the urine causing polyurea .During this stage, azotemia, anemia, and hypertension begin to appear (Sasaki *et al.*,2003). Conservative treatment help in managing the effects of impaired function (Kasper *et al* .,2005). The few remaining nephrons that constitute the functional reserve of the kidneys can be easily disrupted, after which renal failure progresses rapidly (Yu., 2003;Fouque *et al.*,2005).

2-2-2-1-3-Renal Failure

Occurs when the GFR is lesser than 20% of normal. The kidneys cannot regulate both the volume and the solute composition of the body fluids. Therefore, edema, metabolic acidosis, and hyperkalemia develops. Overt uremia may ensue with neurologic, gastrointestinal, and cardiovascular manifestations (Alebiosu *et al.*,2006).

2-2-2-1-4-End-Stage Renal Disease

ESRD occurs when the GFR is lesser than 10% of normal (Ashley ., 2004). ESRD characterize by reduction in renal capillaries and scarring in the glomeruli ,atrophy and fibrosis are evident in the tubules. The mass of the kidneys usually is reduced. At this phase, treatment with dialysis or transplantation is necessary for survival (Andreoli *et al.*,2004) .

2-2-2-2- Causes Of Chronic Renal Failure

According to US Department of Health and Human Services figure (2-2), the most common causes of CRF are: Diabetic nephropathy, Hypertensive nephrosclerosis ,Glomerulonephritis ,Interstitial nephritis, and Polycystic kidney disease (**Bethesda., 2007**).

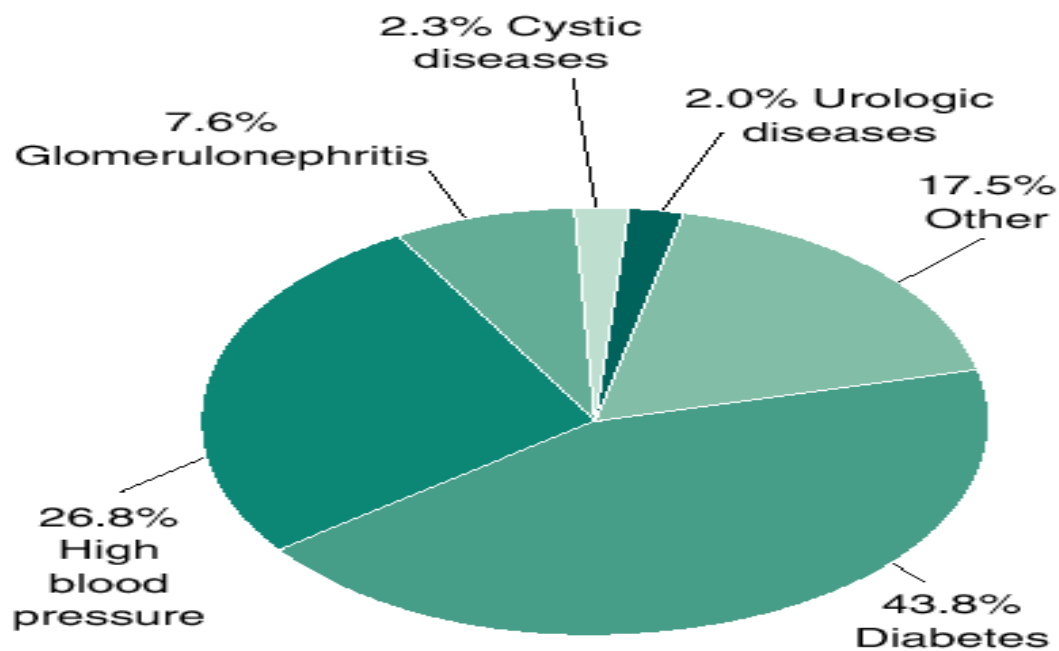


Figure 2-2 The most common causes of CRF (**Bethesda.,2007**)

2-2-2-3-Pathogenesis of CRF

2-2-2-3-1-Retained Metabolic Product

The fact that toxic substances are responsible for the uremic syndrome is supported by:

1. Marked symptomatic improvement occurs after decreasing protein intake which mean that metabolites of protein are retained in renal failure and exert toxic effects (**National Kidney Foundation .,2006**).

2. Effective dialysis results in marked symptomatic improvement . This suggests that toxic metabolites are removed by dialysis (**Kumar & Ahlawat.,2007**).

3. Uremic plasma seriously interferes with a variety of normal cell functions. The same plasma after dialysis has no adverse effects (**Santos et al. ,2005**).Molecules in the molecular weight range of 300-1500 Daltons could be responsible for the uremic state. This has been termed the “Middle Molecule Hypothesis”(Meyer & Hostetter.,2007).

When urea is present in high concentration in the body, it may decompose spontaneously into ammonia and Cyanate . Cyanate is a potential toxin which combines irreversibly with normal proteins in cells and affects their functions (**Lim et al.,1995;Nilsson et al., 1996**). Urea can decompose to substances with potential toxicity. This observation provides support for the chemical basis of the uremic syndrome (**Kraus et al.,2001**).

2-2-2-3-1-1-Overproduction Of Counter-Regulatory Hormones

Overproduction of parathyroid hormone (PTH) and natriuretic hormone could contribute to many aspects of the uremic state.(**Dale & Federman.,2003**). B-type natriuretic peptide (BNP) is a hormone that is released in response to wall stretch of the cardiac ventricles.(**Michael et al.,2004**).N-terminal proBNP (NT-proBNP) is an inactive fragment that is released along with BNP in a 1:1 ratio, cleared renally, and removed by hemodialysis (HD) to a very small extent (**Rosner.,2007**). The levels of both BNP and NT-proBNP are elevated in the ESRD. The prognostic value of BNP or NT-proBNP is less well established in ESRD (**Robert et al.,2006**).

2-2-2-3-1-2-Underproduction Of Renal Hormones:

Decreased erythropoietin (**Alan et al.,2006**) , decreased 1-hydroxylation of vitamin D3 .Clearly, these and other such deficiencies could play a role in the uremic state. (**Spinowitz,2008**).

2-2-2-3-2-Cellular Dysfunction In Uremia

A characteristic feature of nearly every normal cell in the body is a very low concentration of sodium ions (Na^+) in the intracellular water compartment. In contrast, the concentration outside the cell is about 140 mmol/L (**Gannong.,2005**). Under normal conditions sodium ions leak through the cellular membrane into the cell which increases sodium concentration inside the cell which activates the enzyme adenosine triphosphatase(ATPase) which promptly moves sodium from the cell into the extracellular space(**Criddle.,2007 ;Liu & Shapiro ., 2007**).

Advanced uremia results in accumulation of sodium and chloride inside the cell (**Fraser et al.,1985**).This lead to accumulation of water and a fall in potassium concentration and result in alteration in the activity of sodium-potassium ATPase ($\text{Na}^+\text{-K}^+$ ATPase) (**Wood et al.,1990**) .Maintenance dialysis over a period of weeks ameliorates the defect in intracellular Na^+ , and this improvement is contemporaneous with an increase in the number of $\text{Na}^+\text{-K}^+$ pump sites per cell (**Kaji & Thomas ., 1987**). A cell in which these changes take place has been referred to as the sick cell of uremia(**Cheng et al.,2000**).plasma from patients with CRF have an inhibitory effect on $\text{Na}^+\text{-K}^+$ ATPase activity with resultant depression of Na^+ pump activity (**Stokes et al.,1990**). Circulating inhibitors deriving from alimentary protein intake may affect cation transport (**Aparicio et al.,1991**).Retention of salt and water inside the cell occurs early so that a sharp decline in total body weight following initiation of dialysis therapy observed (**Criddle.,2007**).

2-2-2-3-4- Pathophysiology of CRF

2-2-2-3-4-1-Intact Nephron Hypothesis:

Nephrons functioning in diseased kidneys to maintain glomerulo-tubular balance, so that filtration and net excretion of various substances are coordinated(**Wasserstein.,1993;Bennett &Plum,1996**).

2-2-2-3-4-2- The Magnification Phenomenon:

Although nephrons in diseased kidneys function homogeneously, they alter their handling of given solutes as needed to maintain balance of these solutes ,so nephrons can magnify their excretion of a given solute. ((**Dussol et al.,2004**).

2-2-2-3-4-3- Trade-off Hypothesis

The mechanisms that are magnified to maintain individual solute control may have deleterious effects on other systems. This trade-off is seen in the increased PTH secretion seen in CRF which enhances renal phosphorus excretion(**Klahr et al .,1988; Bennett & Plum.,1996**).

2-2-2-3-4-4-Solute handling in CRF .

2-2-2-3-4-4-1- Creatinine and Urea balance.

Creatinine, an amino acid derivative with a molecular mass of 113 Dalton is freely filtered by the glomerulus. Serum creatinine is influenced by inflammation, age, gender and muscle mass, and has limits to detect mild renal impermanent. With the GFR varying between 90 and 60 ml/min/1.73 m², creatinine levels do not significantly increase due to enhanced tubular secretion and glomerular filtration (**Kleber et al.,2007**). Moreover, tubular secretion of creatinine differs among and within individuals. For these reasons, the relationship between creatinine and

GFR varies substantially and creatinine clearance (CrCl) exceeds the GFR (**Stevens et al., 2006**).

Urea is quantitatively the most important solute excreted by the kidney and was the first organic solute detected in the blood of patients with kidney failure(**Lim et al.,1995**). Both HD and peritoneal dialysis are currently prescribed to achieve target values for urea clearance. (**Meyer &Hostetter.,2007**) .

2-2-2-3-4-4-2-Water Balance

In order to maintain water balance, the fraction of water reabsorbed by the kidney must decrease. Thus, an increased flow per nephron ensues. With progressive CRF, the ability to excrete a water load is compromised and the patient may develop hypo-osmolarity (**Nielsen et al.,1999**) . Urine concentration ability of the kidney becomes fixed around 300 mosm/kg of water and thus, a CRF patient is prone to both excess and deficit of water which cause fluid overload and dehydration. (**Patel.,2007**). A common problem in dialysis patients is fluid overload and malnutrition, so that over time muscle mass is replaced by fluid (**Sternby et al.,2001**).

2-2-2-3-4-4-3- Sodium Balance

Normally, renal and hormonal systems maintain the plasma osmolality within tight limits with variability of no more than 1 to 2% . Hyponatremia reflects either defects in these hormonal and renal control mechanisms or water intake that overwhelms them. defects in renal diluting mechanisms, hormonal control of water excretion, excessive sodium losses, and excessive water intake all contribute to the development of hypo-osmolality (**Rosner & Kirven.,2007**).

In order to maintain Na^+ balance in patients with CRF, the fraction of sodium reabsorbed must be decreased. A humeral natriuretic factor in CRF helps to increase Na^+ excretion(**Biesen et al.,2006**). In CRF major increase in sodium intake results in edema and major decreases in intake or increases in extrarenal losses result in volume depletion (**Williams.,2006**).While normal subjects on salt restricted diet reduce urine Na^+ to 20 mEq in 48 hours, CRF subjects may require 1-2 weeks for similar sodium conservation and thus are prone to sodium depletion (**Bourgoingnie et al.,1982**).

2-2-2-3-4-4-4- Potassium Balance

The ratio of intracellular-to-extracellular K^+ concentration largely determines the cell membrane resting electrical potential that, in turn, regulates the function of excitable tissues(**Rachoin & Weisberg.,2008**). This ratio depends heavily on the extracellular K^+ concentration. This equilibrium is modulated by insulin, catecholamines, acid-base balance, plasma tonicity, the parity between K^+ intake and elimination and several other factors (**Ahmed&Wiesberg.,2001**). In normal renal function, the kidneys are responsible for the elimination of about 95% of the daily K^+ load (**Rachoin &Weisberg .,2008**). Inhibition of the renin-angiotensin system in azotemic patient is viewed as a potential cause of severe Hyperkalemia.(**Textor et al.,1982;Reardon & Macpherson .,1998**). In this respect, isolated reports have shown episodes of life-threatening Hyperkalemia (**Chiu et al.,1997**) . Few studies, have shown increased serum K^+ in azotemic patients taking angiotensin converting enzyme ACE inhibitors (ACEIs).(Keilani et al.,1999;Ahuja et al.,2000). The Hyperkalemia is thought to result from aldosterone inhibition secondary to decreased angiotensin-II (AngII) production (**Textor et al., 1982**).

According to this notion, ACEIs should take away the mayor component of K^+ homeostasis in renal failure (**Durant et al.,1988 ;Gracia et al., 2001**).

2-2-2-3-4-4-5-Hydrogen Ion and Acid-Base Balance

The arterial PH is regulated by the control of CO_2 tension ($Paco_2$) through the nervous system and respiratory system while the kidneys control the bicarbonate (HCO_3) by excretion or retention of acid or alkali (**Sheffman.,2001**). Metabolic acidosis is noted in a majority of patients when GFR decreases to less than 20 to 25 % of normal (**Hrabcakova et al.,2002**). The degree of acidosis approximately correlates with the severity of CRF. Metabolic acidosis can be of the high-anion-gap type (**Kraut & Kurtz., 2005**).

2-2-2-3-5-Progression of CRF

2-2-2-3-5-1- Intraglomerular Hypertension And Glomerular Hypertrophy

In animal models, a rise in intraglomerular pressure, due either to the compensatory response to nephron loss or to primary renal vasodilatation appears to play an important role in the progressive glomerular scarring. (**Jungthirapanich et al.,1997**). At least two factors may be involved: Direct endothelial cell damage (**Welch et al.,2007**),and Increased pressure-induced movement of circulating macromolecules through the fenestrated endothelial cells into the subendothelial space in the glomerular capillary wall (**Jungthirapanich et al.,1997;Wolf et al.,2002**).

cytokines such as platelet-derived growth factor and transforming growth factor- β (TGF- β) may play a contributory role(**Fujisawa et al.,2000**). Transforming growth factor beta 1 (TGF- β 1) is implicated in the pathogenesis of diabetic nephropathy (**Yerkey et al.,2004**). In ESRD patients, serum concentrations of TGF- β 1 are reduced, and may result in

accelerated atherosclerosis (**Stefoni et al.,2002**). Studies, suggest that TGF- β may contribute to the development of glomerulosclerosis in a variety of renal diseases (**Nony & Schnellmann ., 2003**) .

2-2-2-3-5-2- Other Secondary Factor

2-2-2-3-5-2-1- Phosphate Retention

In patients with CRF, hyperphosphatemia is observed at GFR levels below 40 ml/min/1.73m² (**Norman et al.,2000**) and almost always in patients on dialysis. Hyperphosphatemia has several deleterious effects on PTH secretion (**Kilav et al.,1995**), parathyroid cell proliferation (**Naveh-many et al.,1995**) and vascular calcification (**Oh et al.,2002**).

2-2-2-3-5-2-2- Altered Prostanoid Metabolism

Glomerular prostaglandin production tends to be increased in glomerular disease(**Arima et al.,1994**). This response may produce renal vasodilatation to maintain the GFR in the presence of an often marked reduction in glomerular capillary permeability (**Kopecky & Schroeder.,1988**). These changes are manifested clinically by reductions in GFR and protein excretion in many patients with chronic glomerular disease (**Imanishi et al.,2001**).

2-2-2-3-5-2-3-Dyslipidemia

Dyslipidemia is common in patients with CRD, It contributes to glomerular and interstitial injury of the renal parenchyma (**Keane & Lyle .,2005**). Studies suggest that high lipid levels accelerating the development of systemic atherosclerosis and may promote progression of the renal disease(**Kasiske et al., 1990; Schaeffner et al.,2003**). Cholesterol loading in experimental animals enhances glomerular injury, glomerulosclerosis and tubulointerstitial damage (**Kasiske et al.,1990**).. On the other hand lipid lowering drugs such as statins slows the rate of

progressive renal injury (**Guthrie & Martin ., 2007 ;Strippoli et al.,2008**). Dyslipoproteinemia observed in these patients contributes to the progression of glomerular and tubular lesions, with subsequent deterioration to ESRD (**Schaeffner et al.,2003**). The contribution of this complex atherogenic form of dyslipidemia to CVD in patients with renal disease is important to reduce the coronary and renal complications (**Keane&Lyle.,2005**) . Some studies have reported negative results regarding the predictive power of serum lipids for the development of CVD (**Wanner & Krane., 2002**).Roughly two thirds of all patients with ESRD and kidney transplants suffer from dyslipidemia and should receive lipid-lowering therapy(**Karie et al.,2006**) .The most prominent changes in CRF are increased serum triglycerides (TG) levels and low levels of high-density lipoprotein (HDL) cholesterol (**Vaziri.,2005**). Low-density lipoprotein (LDL) cholesterol levels are often normal (**Fried et al.,2001**) .The apolipoprotein B-containing part of the lipoprotein may undergo modifications (**Cibulka & Racek ., 2007**).Serum TG are elevated in CKF because of enhanced production of TG-rich lipoproteins such as very-low-density lipoproteins (VLDL) in the liver and dysfunction of TG degradation resulting from insufficient mitochondrial beta-oxidation of fatty acids (**Schaeffner et al.,2003**). In addition to its role in reverse cholesterol transport, HDL has the ability to protect LDL particles against oxidation. The underlying mechanism by which HDL inhibits LDL oxidation is partly enzymatic .(**Dantoine et al.,1998;Gutierrez et al.,2000**).There is a linear correlation between body mass index (BMI)and survival in dialysis patients , to the extent that the usual association of increased mortality with obesity is reversed in patients who receive renal replacement therapy (**Wynne et al.,2005;Kalantar-Zadeh et al.,2007**).

2-2-2-3-5-2-4- Proteinuria

Proteinuria itself may contribute to disease progression, both by overloading the mesangium with macromolecules and by promoting tubulointerstitial disease (**Rosolowsky et al.,2008**). It is possible that a marked increase in protein filtration and subsequent proximal reabsorption leads to tubular cell injury and the release of lysozymes into the interstitium (**Jefferson et al.,2008**).Thus, reversing intraglomerular hypertension with protein restriction or antihypertensive therapy may be beneficial both by diminishing hemodynamic injury to the glomeruli and by reducing protein filtration (**Wasserstein.,1993**).

2-2-2-3-5-2-5- Tubulointerstitial Disease

CRF associated with marked tubulointerstitial injury even if the primary process is a glomerulopathy (**Kaynarsafak et al.,2005**). The degree of tubulointerstitial disease is a better predictor of the GFR and long-term prognosis than is the severity of glomerular damage (**Reichert et al.,1999**). Both calcium phosphate deposition and metabolic acidosis may play a contributory role in the development of tubulointerstitial disease. (**Kaynarsafak et al.,2005**). Healing may be associated with interstitial fibrosis mediated in part by the release of cytokines such as TGF- β (**Harendza et al.,1999**).

2-2-2-3-5-2-6- Retained Toxins

Dialysis of nonnumeric animals with glomerulosclerosis preserves the GFR and slows the rate of further glomerular damage. (**Takamura et al.,1997**).

2-2-2-3-5-2-7- Iron Toxicity

Increased glomerular permeability can result in the filtration of the normally nonfiltered iron-transferrin complex. Dissociation of this complex in the tubular lumen leads to the release of free iron which can

promote tubular injury by promoting the formation of hydroxyl radicals(**Parkash.,2007**).

2-2-2-3-6-Clinical Manifestations Of CRF

The manifestations of CRF are manifested in Fig. 2-3. (**Skorecki et al.,2001**) There currently are four target populations that comprise the entire population of CRF: persons with chronic renal insufficiency, those with CRF treated with HD, those being treated with peritoneal dialysis, and renal transplant recipients (**Flanigan.,2008**).

2-2-2-3-6-1 Neurological Disorders:

2-2-2-3-6-1- 1 Disorders of Neural Function

These include alterations in peripheral and nervous system function ,peripheral neuropathy. The associated neuropathy can contribute to muscle weakness and atrophy in CRF patients(**Brouns & De Deyn.,2004**). Peripheral neuropathy affects the lower limbs more frequently. It is symmetric and affects both sensory and motor function. (**Brouns &De Deyn.,2004**). Neuropathy is caused by atrophy and demyelination of nerve fibers, caused by uremic toxins. Restless legs syndrome is a manifestation of peripheral nerve involvement and can be seen in two thirds of patients on dialysis(**Miranda et al.,2001**).This syndrome is characterized by creeping, prickling, and itching sensations that typically are more intense at rest (**Siddiqui et al., 2005 ;Cotter&Keeffe.,2006**). Temporary relief is obtained by moving the legs. A burning sensation of the feet, which may be followed by muscle weakness and atrophy, is a manifestation of uremia (**Collado-seidel et al.,1998**). Sleep disorders such as sleep apnea in such patients ranges from 50 % to 70 % (**Hanly & Pierratos ., 2001**).

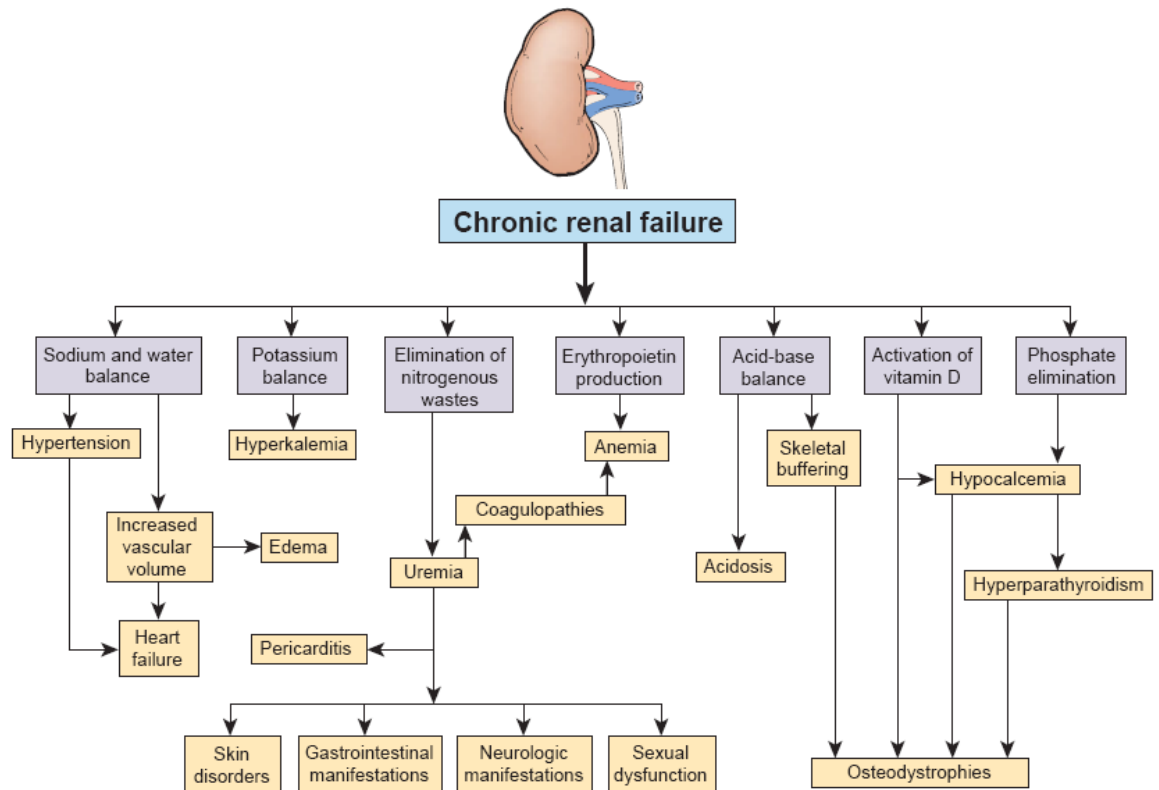


Figure 2-3: Manifestations of chronic renal failure (Skorecki *et al*,2001).

CNS disturbances in uremia referred to as uremic encephalopathy (**Brouns &De Deyn.,2004**). The condition may result from an excess of toxic organic acids and electrolyte abnormalities. Reduction in alertness is the earliest and most significant indication of uremic encephalopathy (**Mahoney *et al*.,1984**). These often are followed by loss of recent memory, delirium ,coma and seizures are (**Bourne &Teschan.,1983**).

2-2-2-3-6-1-2 Psychological Disorders

Emotional trauma frequently follows any disaster .One such disease is ESRD (**Lancaster., 1995**). Emotional trauma may include flashbacks when events trigger suppressed memories or unresolved emotions. (**Clellan.,2001**). Depression is more common among patients with ESRD

due to changes in endocrine, neurologic, hemostatic, and immune function(**Boulware et al.,2006**).

2-2-2-3-6-2-Hematologic Disorders

2-2-2-3-6-2-1- Anemia

Chronic anemia is the most profound hematological alteration that accompanies renal failure. Anemia first appears when the GFR falls below 40 ml/min (**Tong & Nissenson.,2001**). Nephrologists have defined clinically significant anemia as a hemoglobin level (Hb)< than 10 g/dL and a hematocrit of less than 30%, in the absence of erythropoietin therapy (**Besarab & Levin .,2000**). An analysis of patients beginning dialysis in the United States found that 67% had a hematocrit of less than 30%, and 51% had a hematocrit of less than 28% (**Obrador et al., 1999**).

The kidneys are the primary site for the production of erythropoietin, which controls RBCs production. In CRF, erythropoietin production usually is insufficient to stimulate adequate RBCs production by the bone marrow(**Jones et al.,2005**). The accumulation of uremic toxins further suppresses RBCs production in the bone marrow, and the cells that are produced have a shortened life span (**Ly et al.,2004**). abnormal coagulation due to decreased platelet function and marrow space fibrosis occurs (**Rao et al.,1993;Kozek-Langenecker et al.,1999**). Iron deficiency is the most common cause of hyporesponsiveness to erythropoiesis-stimulating agents (ESAs) in ESRD patients (**Horl et al.,2007**). Many persons on maintenance HD also are iron deficient because of blood sampling , anorexia , dietary restrictions and accidental loss of blood during dialysis(**Tinmouth et al.,2008**).Anemia causes tissue hypoxia and may lead to severe cardiovascular, neurological, and musculoskeletal malfunction including weakness, fatigue, depression, insomnia, and decreased cognitive function (**Tanner et al**

.,2002;Angelillo-scherrer *et al.*,2008) .Anemia of CRF produces a decrease in blood viscosity and a compensatory increase in heart rate, decreased vascular resistance and exacerbates peripheral vasodilatation. Echocardiographic studies shown ventricular dilatation with compensatory left ventricular hypertrophy (**Tong & Nissenson ., 2001**). Anemia also limits myocardial oxygen supply, leading to angina pectoris and other ischemic events(**Besarab & Levin .,2000**). Thus, anemia, when coupled with hypertension, may be a major contributing factor to the development of left ventricular dysfunction and congestive heart failure in persons with ESRD (**Tanner *et al.*,2002**).

Medical management of ESRD with recombinant human erythropoietin (rhEPO) help to maintain hematocrit levels in the range of 28% to 33%, with an upper limit of 36%(**Kautz *et al.*,2000 ; National Kidney Foundation 2001; Takama *et al.*,2007**) . rhEPO also cause improvement in appetite, energy level, sexual function, skin color, hair , nail growth, and reduced cold intolerance(**Paoletti & Cannella ., 2006**). Because worsening of hypertension and seizures have occurred when the hematocrit was raised too suddenly, frequent measurements of hematocrit are necessary (**Schröder &The European Pediatric Peritoneal Dialysis Working Group.,2003**).

Iron supplementation often is needed specially for those treated with rhEPO (**Mircescu *et al.* ,2006**). Iron can be given orally or intravenously (**Michael *et al.* ,2004**) .

2-2-2-3-6-2-2- Coagulopathies

Bleeding disorders are manifested by epistaxis, menorrhagia, gastrointestinal bleeding, bruising of the skin and subcutaneous tissues (**Kazatchkine *et al.*,1976**). Although platelet production often is normal in ESRD, platelet function is impaired. Coagulative function improves with dialysis but does not completely normalize, suggesting that uremia

contributes to the problem (**Remuzze et al.,1977**). Anemia may accentuate the problem (**Eberst & Berkowitz.,1993**). Anticoagulation is required during HD session which may interferes with plasmatic coagulation, platelet activation. Regional anticoagulation with citrate emerges as the most promising method (**Joannidis & Oudemans-van.,2007**).

2-2-2-3-6-3- Cardiovascular Disorders

It is the major cause of death in patients with ESRD (**Bibbins-domingo et al.,2004**) .The overall mortality rate from CVD in CRF patients is 30 times that of the general population. (**National Kidney Foundation Task Force on Cardiovascular Disease., 1998**).The main CVD are Pericardaitis, hypertension, congestive heart failure, coronary artery disease, cardiomyopathy.

2-2-2-3-6-3-1- Hypertension

HT is an early manifestation of CRF. It may result from an increased vascular volume, elevation of peripheral vascular resistance, decreased levels of renal vasodilator prostaglandins, and increased activity of the renin-angiotensin system (**Preston et al., 1996**) . HT occurs in 80% to 90% of patients with renal insufficiency (**Rodicio&Alcazar.,2007**). Several factors contribute : a. Expansion of extracellular fluid volume (**Simon ., 1990**).b. Increased activity of the renin-angiotensin system (**Johnson et al,1992**).c. Dysfunction of the autonomic nervous system (**Agarwall., 2005**).d. Possible diminished presence of vasodilators: there may be decreased renal generation of prostaglandins or of factors in the kallikrein-kinin system (**Ling et al.,2008**).

2-2-2-3-6-3-2- Heart Disease

The majority of deaths in ESRD are from CVD (**Sarnak et al.,2003**). Left ventricular hypertrophy(LVH) and left ventricular systolic dysfunction are highly prevalent in patients with ESRD and are associated with poor cardiovascular outcomes (**Kennedy et al.,2003 ;Satyan et al.,2007**). Anemia and HT have an independent role in the genesis of left LVH and subsequent CVD (**Jaradat & Molitoris ., 2002**) . People with CRF tend to have an increased prevalence of left ventricular dysfunction, with both depressed left ventricular ejection fraction, and impaired ventricular filling (**Levin & Foley.,2000 ; Al-Ahmad et al.,2001**). Altered calcium / phosphorus metabolism, may result in metastatic calcification of coronary vessels and valves (**Mark & Sarnak.,2003**).

2-2-2-3-6-3-3- Pericarditis

Pericarditis occurs in approximately 20% of CRF patients (**Gunukula & Spodick ,2001**). Uremic pericardial effusion is an expected complication in CRF. patients presented with hypotension , tachycardia ,sever chest pain and pericardial friction rub, which suggested pericardial tamponade. drainage, may yield hemorrhagic pericardial fluid attributed to a coagulopathic state of uremic disease . It can result from metabolic toxins associated with the uremic state or from dialysis(**Kasacka et al.,2004**).

2-2-3-6-4-Pulmonary Disorders

This may result from uremic toxins volume overload, anemia, immune suppression, extra osseous calcification, malnutrition, electrolyte disorders, and acid base imbalances (**Prezant., 1990;Kasacka et al ., 2004**). pleural disease may be common in patients with CRF due to : (1) chronic heart failure; (2) increased risk of infection(3) diseases associated with renal and pleural manifestations; (4) uremic pericarditis (5) increased risk for certain malignancies (**Cohen & Sahn.,2001**) .

Hypoalbuminemia decreases plasma oncotic pressure and thus fosters movement of fluid out of the pulmonary capillaries (**Pierson., 2006**). Pulmonary congestion in CRF is associated with a restrictive pattern on pulmonary function testing. and accounts for “uremic lung” (**Gavelli & Zompatori.,1997**).Pleural effusion is a frequent complication in HD patients(**Ruiz et al.,2005**) When the work-up of a pleural effusion in HD patient does not identify a specific cause, it is usually attributed to uremic pleurisy(**Yoshii et al.,2001**).

2-2-3-6-5-Gastrointestinal Disorders

Poor appetite is common in patients with CRF due to abnormal taste sensation (**Rees &Shaw.,2007**). Appetite is also affected by cytokines (**Mak et al. , 2005**). Cachexia, which implies replacement of muscle with fat and declining plasma proteins, may be more appropriate term in CRF (**Mak et al.,2006**). It may result from anorexia , acidosis and inflammation which cause elevated levels of cytokines such as leptin, TNF- α , IL-1 and IL-6. These act through the hypothalamus to affect appetite and metabolic rate and maintain the constancy of fat stores (**Daschner et al.,1998**).Nausea, vomiting, gastroenteritis, GIT bleeding, and peptic ulcers are common in CRF (**Langbakke et al.,2007**). Decomposition of urea by intestinal flora, resulting in a high concentration of ammonia with associated increase in gastric acid secretion and contributes to gastrointestinal manifestation (**Taylor et al.,1980**).

2-2-3-6-6 Bone, Calcium, Phosphorus Disorders

2-2-3-6-6-1 Mineral And Bone Disorders

Abnormalities of calcium, phosphate, and vitamin D metabolism occur early in the course of chronic renal failure(**Malluche et al.,1976**). Renal osteodystrophy(ROD) refer to the skeletal complications of ESRD (**Hrusks & Teitelbaum .,1995 ; Llach & Bover .,2000**).The main

factors for the development of ROD are disturbances in the calcium phosphate homeostasis, in vitamin D and parathyroid hormone metabolism as well as alterations in the somatotroph axis (**Klaus et al., 2006**). Changes that occur with renal failure have been divided into two major types of disorders that results from abnormal reabsorption and defective remodeling of bone (**Cotran et al., 1999**).

High–bone-turnover osteodystrophy, (steitis fibrosa) is characterized by increased bone resorption and formation, with bone resorption predominating (**Hrusks & Teitelbaum ., 1995**).

Low–bone-turnover osteodystrophy is characterized by decreased numbers of osteoblasts and low or reduced numbers of osteoclasts, a low rate of bone turnover, and an accumulation of unmineralized bone matrix (**Couttenye et al. , 1999**). High turnover bone disease due to enhanced PTH secretion from hyperplasic parathyroid glands was the main cause of renal osteodystrophy, normalization of PTH levels in these patients leads to adynamic bone disease (ABD) with reduced bone formation and resorption (**Hercz et al ., 1993**). Increase in the prevalence of ABD and low PTH levels are frequently seen in CRF patients with ABD(**Astumi et al., 1999**). In addition, ABD is associated with increased fracture rate , brittle calcium control and increased vascular calcification (**Assry et al., 1973; Kruz et al., 1994; Hutchison et al., 1994**). the pathogenesis of ABD has not been fully elucidated, mainly due to a lack of appropriate rat models(**Kazama et al., 2002; Tanaka et al., 2004**). Several vitamin D analogs that prevent hyperactivity of the parathyroid gland without induction of hypercalcemia and hyperphosphatemia have recently become available (**Albaaj & Hutchison , 2003**). It was discovered that accumulation of aluminum from water used in dialysis and aluminum salts used as phosphate binders caused osteomalacia and adynamic bone disease (**Couttenye et al. , 1999**). Early treatment

of hyperphosphatemia and hypocalcemia is important to prevent or slow long-term skeletal complications(**Slatopolsky et al.,2000**).

2-2-3-6-6-2 Vitamin D Metabolism

Vitamin D₃ is initially hydroxylated in the liver by 25-hydroxylase to form 25-hydroxyvitamin D₃, with a subsequent hydroxylation in the kidney to form the active metabolite, 1 α -25-dihydroxyvitamin D₃ (**Carlberg et al .,2001;Tian et al.,2006**). Several tissues have 25-hydroxyvitamin D 1 α -hydroxylase, which could convert 25-hydroxyvitamin D₃ to 1,25 dihydroxyvitamin D₃ locally (**Zehnder et al,2001**) .However, the serum level of 1,25 dihydroxyvitamin D₃ is regulated by renal 25-hydroxyvitamin D 1 α -hydroxylase. calcitriol deficiency (defined as serum levels <22 pg/ml) was found in 32% of CKD stage 3 and >60% of CKD stages 4 and 5 pre-dialysis patients (**Brown.,1998;Malluche et al.,2002**). Vitamin D₃ endocrine system may also be involved in regulating the immune systems, cellular growth, differentiation and apoptosis (**Dusso &Brown. ,1998; Dusso et al.,2005**).Vitamin D₃ levels begin to drop early in the course of kidney disease, leading to elevated PTH levels and disrupted mineral metabolism. (**Rahman et al.,2005 Raggi & Kleerekoper.,2008**).

2-2-3-6-6-3 Phosphate Metabolism

Kidney is principally responsible for phosphate homeostasis, by modulating urinary phosphate excretion. Phosphate is filtered by the glomerulus and subsequently re- uptake in the proximal tubules, which is the rate-limiting step (**Prie et al.,2002**). In CRF, hyperphosphatemia is observed at GFR levels below 40 ml/min/1.73m² (**Noman et al.,2000**).

Increased phosphate levels stimulate PTH secretion in vitro (**Almaden et al.,1996**). Furthermore, a reduction of serum phosphate results in a parallel reduction of PTH levels without change in serum calcium (**Yi et al.,1995**) . Some studies found an increased risk of death for serum phosphate exceeding 2.09 mmol/l in adult patients(**Block et al.,1998**) other studies described a much lower phosphate level (~1.4–1.6 mmol/l) at which a higher incidence of calcifications was found (**Ribeiro et al.,1998**). In renal patients, extensive calcification of the tunica media occurs even after short periods of dialysis, as shown by investigations of the epigastric artery in adult patients (**Moe et al.,2002**). Animal experiments demonstrated that a high plasma phosphate levels cause accelerated cardiac fibrosis(**Amann et al.,2003**).

2-2-3-6-6-4 Calcium Metabolism

under normal conditions, serum calcium fluctuates by a maximum of 2% either side of normal (**Brown.,2000**). inverse relationship between serum levels of PTH and calcium illustrates an exquisitely sensitive control mechanism in which only minute changes in serum calcium are required to induce large changes in PTH (**Massry & Coburn.,2003**). Calcium and phosphorus homeostasis are disturbed relatively early in the course of CKD. This, together with a decrease in calcitriol production, leads to the elevated PTH levels that typify secondary hyperparathyroidism (SHPT). (**Tallon et al.,1996**). In ESRD, higher PTH concentrations are required to maintain calcium homeostasis (**Hendy et al.,1989;Ritz et al.,1991;Yoshiko et al. , 2005**). Accumulation of phosphorus due to the decreased glomerular filtration rate is another important factor in the pathogenesis of SHPT (**Rodriguez et al.,1996;Delmez & Slatopolsky .,1992**). High serum phosphorus

prevents the reduction in PTH induced by calcitriol administration (**Rodriguez et al.,1991-A**). In addition, high phosphorus levels impair the calcemic action of PTH, which is another cause of hypocalcemia in renal patients (**Rodriguez et al.,1991-B**)

2-2-3-6-7 Skin Disorders

The skin often is pale due to anemia (**Morton et al.,1996**). Dryness of skin and mucous membranes, subcutaneous bruising, increase serum histamine due to allergic sensitization to various dialyzer membrane components and due to impaired renal excretion of histamine(**Elter & Myers.,2002**). Purities is common due to high serum phosphate levels (**Bencini et al ., 1985 ; Elter & Myers ., 2002**). Severe scratching and repeated needle sticks, especially with hemodialysis, break the skin integrity and increase the risk for infection (**Udayakumar et al.,2006**). hyperpigmentation on sun-exposed areas is attributed to failure of the kidneys to excrete beta-melanocyte-stimulating hormone (b-MSH) (**Smith et al.,1976; Imazu et al.,1993**). Uremic fetor is an ammoniacal odor caused by a high concentration of urea in the saliva and its breakdown to ammonia (**Astback et al.,1999**).

2-2-2-3-6-8 Sexual Dysfunction

The cause of sexual dysfunction in CRF is unclear is multifactorial and may result from high levels of uremic toxins, neuropathy, altered endocrine function, psychological factors, and medications. Impotence occurs in as many as 56% of male patients on dialysis (**Rickus .,1987; Fung et al.,2004**).Decreases in testosterone levels and increases in prolactin and luteinizing hormone levels, are common and cause erectile difficulties and decreased spermatocyte counts (**Adames &Vaziri.,2006**). The prevalence of erectile dysfunction in patients in hemodialysis program can reach 60 %. (**Messina et al.,2007**).

Several drugs, such as exogenous testosterone and bromocriptine, have been used in an attempt to return hormone levels to normal. Impaired sexual function in women is manifested by abnormal levels of progesterone, luteinizing hormone, and prolactin. Hypofertility, menstrual abnormalities, decreased vaginal lubrication, and Amenorrhea is common among women who are on dialysis therapy(**Foulks & Cushner .,1986**).

2-2-2-3-6-9 Altered Immune Function

Uremia is associated with various immune defects such as depressed peripheral lymphocyte count, impaired granulocyte phagocytic ability, monocytes dysfunction and T cell pre-activation, (**Meuer et al. ,1987**). Uraemic toxins as well as continuous blood–membrane contact during HD sessions contribute mainly to the immune dysfunction in patients with CRF (**Tsakiris et al.,1999**). Immune dysfunction may be manifest early in the course of renal insufficiency (**Goldblum & Reed., 1980**). After CVD, infections are the second most common cause of death in HD patients and lead frequently to hospitalization (**Powe et al.,1999; U S Renal Data System .,2003**).Mortality risk due to sepsis is about 250-fold higher among HD patients than in the general population (**Sarnak &Jaber.,2000**). Furthermore, immune dysfunction is reflected by a poor vaccination response against T helper dependent antigens, e.g. hepatitis B or influenza (**Cavdar et al .,2003;Friedman et al.,1980**). Some studies have suggested that the antigen-presenting function of monocytes is impaired in CRF (**Koehler et al.,1984**). Later new findings demonstrated a defective immunological pathways in HD patients caused by a diminished expression of CD86 on monocytes (**Girndt et al.,1993; Girndt et al.,2001**). The circulating levels of interleukin-6 (IL-6) are elevated in response to dialysis (**Kaizu et al.,1998; Borazan et**

al.,2004).Tumor necrosis factor (TNF-) levels are also elevated in ESRD patients both before and after hemodialysis (**Prie et a l., 2002**).

IL-6 and TNF- are known to induce muscle wasting (**Barton .,2001;Raj et al.,2004**).

2-2-2-3-6-10 Metabolic syndrome

It is characterized by abdominal obesity, dyslipidemia, hypertension, and hyperglycemia (**Kurella et al.,2005**). The metabolic syndrome is associated with CKD and microalbuminuria (**Iseki et al.,2004;Chen et al.,2007**). Insulin resistance is characteristic feature (**Bhowmik &Tiwari., 2008**). Hyperinsulinemia leads to increased sodium and uric acid reabsorption by the tubules leading to hypertension and hyperuricemia. Ultimately there is β -cell burn out and development of diabetes (**Kitiyakara et al.,2008**).

2-2-2-4 Management Of Chronic Renal Failure

Risk factors for CKD include an age of more than 60 years, HT, DM, CVD, and a family history of the disease(**Stevens et al.,2006**). Measurement of urine albumin and GFR are important to evaluate people at risk (**Levey et al.,2005**). It is important to recognize and to treat the primary renal disease such as glomerulonephritis, membranous glomerulonephronopathy or analgesic nephropathy are potentially treatable or can be stabilized (**Stigant et al.,2003**).Early detection of renal disorders is important to prevent further injury and progressive loss of renal function (**Pamar.,2002**). About 20-30 patients have some degree of renal dysfunction for each patient who needs renal replacement treatment.(**Jones et al.,2000**). Diabetes and hypertension are the two

most common causes of ESRD and are associated with a high risk of death from CVD (**Michael et al.,2008**).Current care recommendations might include:

Meticulous control of blood glucose has been conclusively shown to reduce the development of microalbuminuria by 35% in type 1 and type 2 diabetes (**The diabetes control and complications trial research group.,1995**). Glycaemic control can reduce the progression of diabetic renal disease.(**Wang et al.,1993**) Adequate control of HT has been shown to delay the progression of albuminuria in DM (**Brenner et al.,2001, Karalliedde et al.,2008**) . Angiotensin receptor blockers have been shown to have renoprotective effects in both early and late nephropathy due to type 2 diabetes.(**Lewis et al.,2001; Li., 2001 ; Parving et al.,2001**).

The optimal level of BP control is uncertain, but diastolic pressures of < 80 mmHg may be desirable.(**Stigant et al.,2003;Contreras et al .,2005**) .ACEIs appear to be more effective in slowing GFR decline.(**Sarnak et al .,2005; Gassman et al.,2003 ;Wright et al .,2002**). The change in the level of proteinuria is a predictor of subsequent progression of hypertensive kidney disease at a given GFR (**Morris., 2004**).Therefore even normotensive patients should be treated if they have proteinuria (**Yeung et al.,2006**).

Protein intake should be restricted to 0.8 to 1 g/kg of high biologic value protein (**Wasserstein.,1993**), treatment of hyperphosphatemia with calcium carbonate or calcium acetate(**Yi et al.,1995**), both hyperlipidemia and metabolic acidosis should be treated(**Boirie.,2000**).Patients with advanced CRF are at increased risk for depletion of calcium , iron , zinc , vitamin B₆, vitamin C and folic acid ,vitamin D (**Kopple.,1999**).

2-2-2-4-1 Treatment Of End Stage Renal Failure

When GFR falls below 5 ml/min, the patient usually can not live without renal replacement therapy in order to remove accumulated toxins and fluid over load (**Maisel &Stevenson.,2002; Ashley.,2004**). There are two broad categories of dialysis :hemodialysis and peritoneal dialysis

2-2-2-4-1-1 Hemodialysis

Introduction of this treatment has dramatically extended life in patients with severe renal failure. (**Suri et al.,2006**) The principle is simple. The patient's blood is withdrawn from the circulation and passed through tubing surrounded by a dialysate fluid. The tubing is permeable to water and to the smaller particles in the blood, including ions, glucose, urea and creatinine, but the tubing does not allow plasma proteins and cellular elements to be lost from the blood (**Sternby .,2001; Flanigan.,2008**). The dialysate fluid is free of unwanted items such as urea and contains appropriate amounts of various ions (**Saito et al.,2003**) . a dialysate is much different from the sophistication of normal renal function with its filtration, reabsorption, excretion, medullary osmotic gradient, complex vasculature and hormonal control (**Himmelfarb .,2006**). The patient's blood with dialysis required two or three times per week for (**Eknoyan et al.,2002**). *Arteriovenous shunt* was uncomfortable with risk of bleeding (**Schon &Whittman.,2003;Asif et al.,2006**). then, a *surgical arteriovenous fistula* was devised (**Hoggard et al.,2008**).

2-2-2-4-1-2 Peritoneal dialysis

This is an alternative to HD, it uses the capillaries of the peritoneal cavity as the tubing, and fluid passed into the peritoneal cavity and withdrawn after an equilibration period as the dialysate (**Diaz-Buxo.,2001**). In practice, fluid is kept in the peritoneal cavity almost continuously (**Haq&Nolph.,2001**).

4.1.History of the patients

4.1.1 Sex differences in CRF

The patients under study were divided according to sex deference to male (41patients) and female(22 patients) groups. male to female ratio was 1.8:1 . males constitute 65% of patients with CRF on hemodialysis ,while the females constitute only 35% of the patients figure 4-1 .

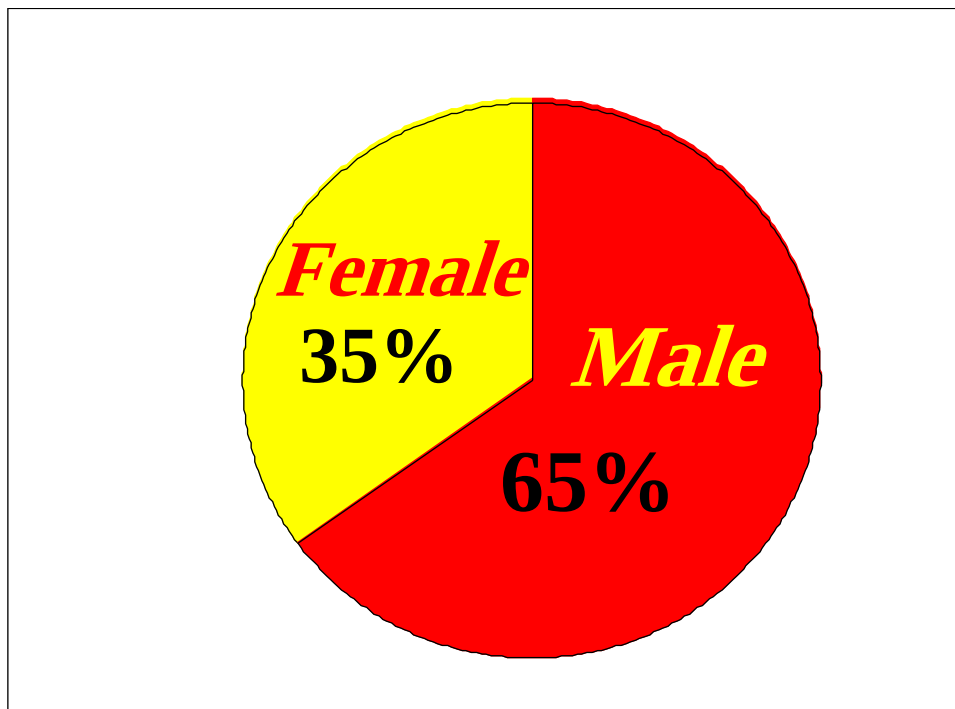


Figure 4-1: Male to Female ratio in patients with CRF.

4.1.2 Age prevalence in CRF

The patients under study were divided according to age in to six groups the most higher incidence of CRF observed in the 40s figure 4-2

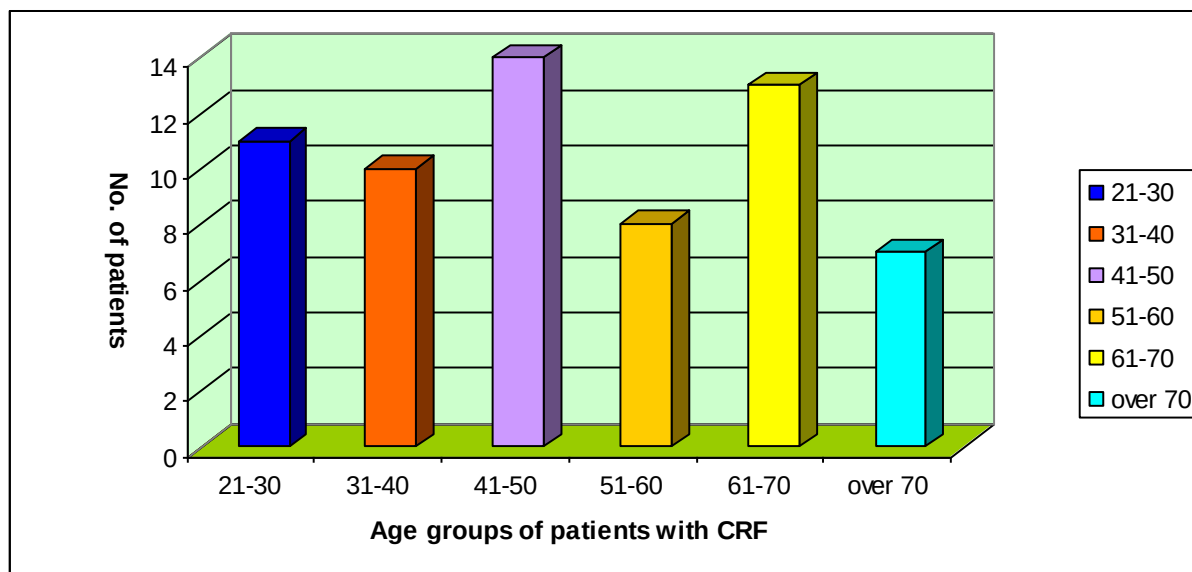


Figure 4- 2: Age distribution in patients with CRF.

4.1.3 Blood groups prevalence in CRF

The patients with CRF who were under study divided according to their blood groups .The higher incidence of CRF were found in blood group O+ve who constitute 43% of the patients on hemodialysis figure 4-3.

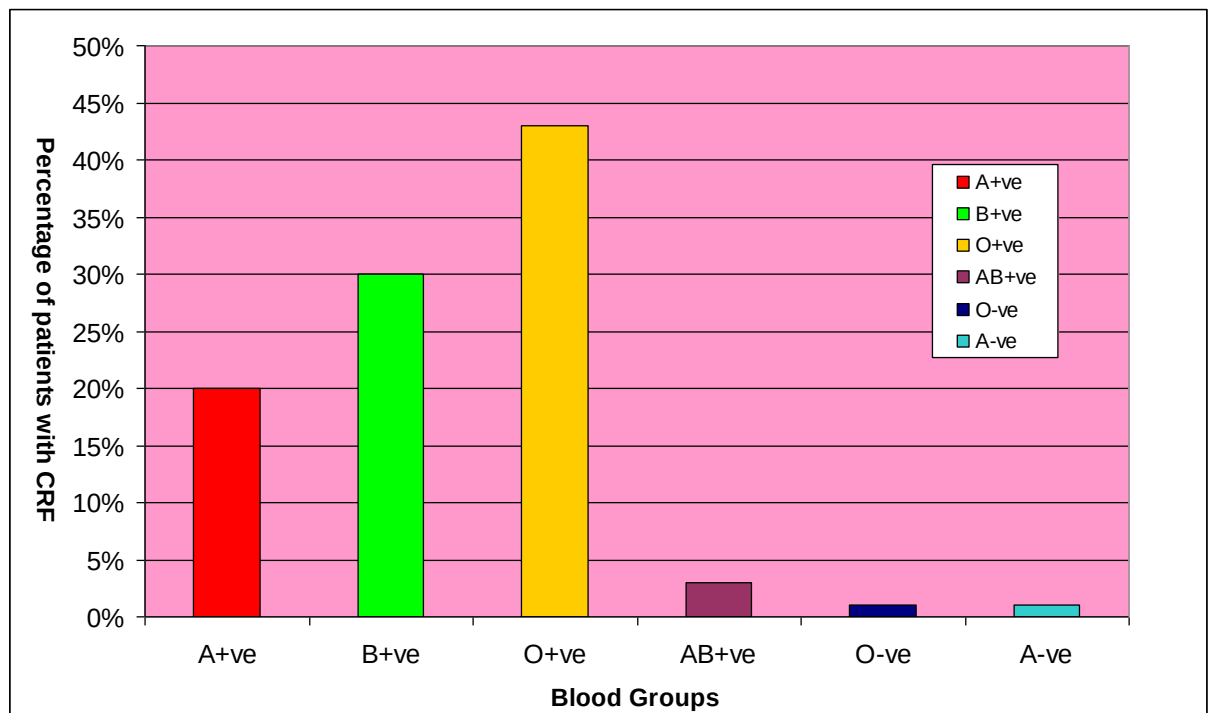


Figure 4-3 Blood groups distribution in patients with CRF.

4.1.4. Smoking prevalence in CRF

According to patients history 37 patients with CRF were smokers who constitute 58% and 26 of them were non smokers who constitute 42% figure 4-4 .

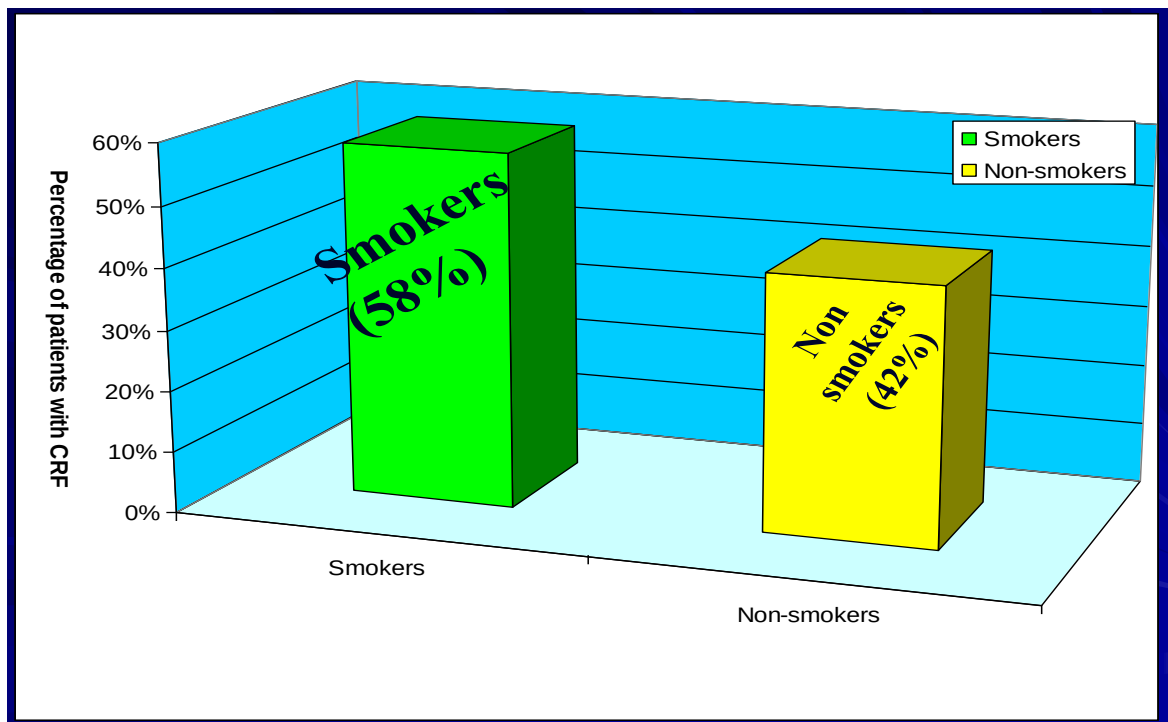


Figure 4-4 :The ratio of smokers to non smokers in patients with CRF

4.1.5. Chronic disease prevalence in CRF

According to the history there were 23 CRF patients present with a history of diabetes mellitus who constitute 36% of CRF patients on hemodialysis .There were 33 patients presented with a history of hypertension who constitute 52% of CRF patients on hemodialysis . There were 11 patients presented with a history of ischemic heart disease who constitute 17% of CRF patients on hemodialysis . There were 5 patients presented with a history of benign prostatic hypertrophy who constitute 7% of CRF patients on hemodialysis figure 4-5 .

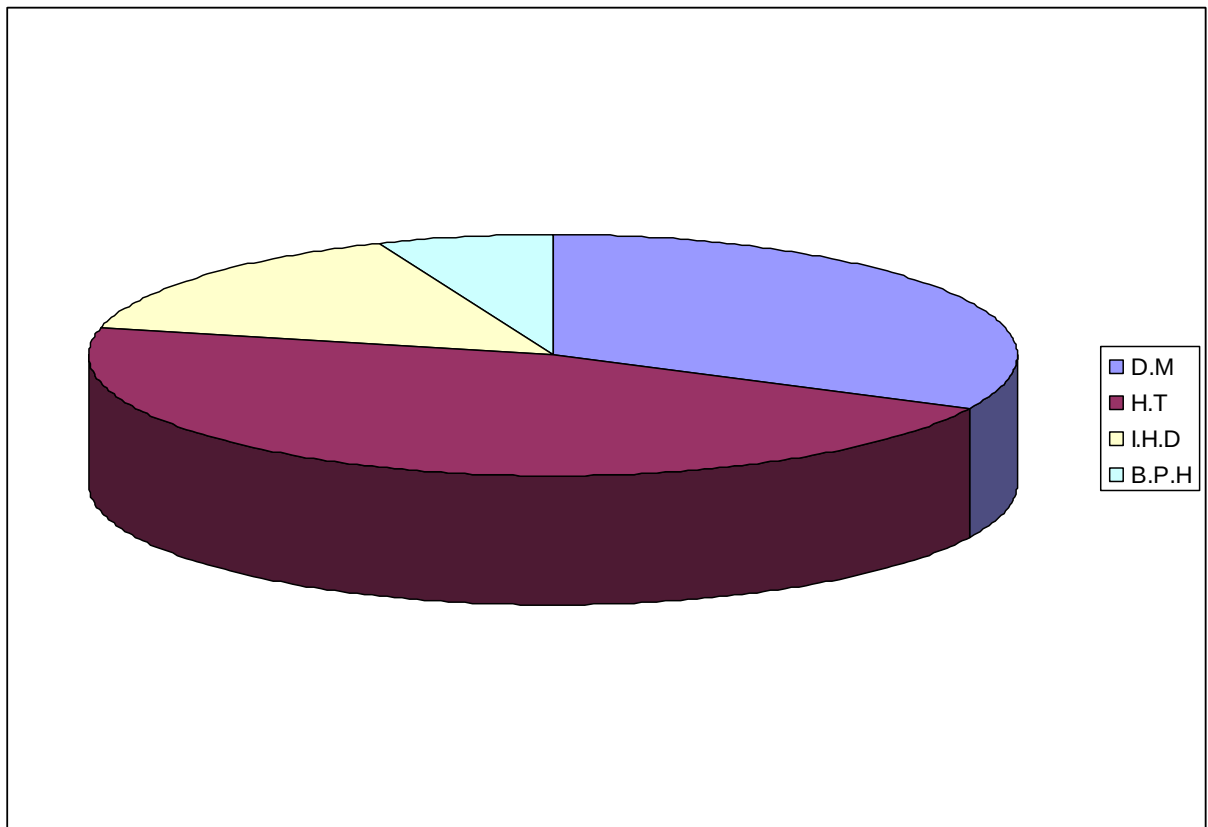


Figure 4-5 Distribution of chronic diseases in CRF patients

4.2 The Biochemical parameters Results according to sex difference

4.2.1 Urea ,Creatinine ,Uric acid and Sugar

There was a significant increase in urea concentration in male and female patients relative to the male and female control at $p < 0.001$. On the other hand there was a significant increase in Creatinine concentration in male and female patients relative to the male and female control at $p < 0.001$ (Table 4.1).While there was a significant increase in Uric acid concentration in male and female patients relative to the male and female control at $p < 0.01$. There was no significant

difference in glucose concentration between the patients and control subjects at $p > 0.05$ (Table 4.1).

Table (4.1): The urea ,creatinine ,uric acid and sugar concentrations in control and patients with CRF on hemodialysis according to sex difference.

The Biochemical test	Control group No. =63		CRF patients on Hemodialysis=63	
	Male	female	Male	Female
Blood Urea mmol/L	3.629±0.881	3.5518±0.620	31.319±13.38 9 ***	31.427±17.257 ***
S.Creatinine μmol/L	67.341±6.483	35.518±0.620	432.097±199.945 ***	417.272±205.948 ***
Uric acid μmol/L	214.853±32.967	209.454±41.938	266.365±33.557 **	229.772±34.267 **
Blood sugar mmol/L	5.312±1.195	5.336±1.320	5.585±1.603 NS	5.477±1.285 NS

Values are mean ±SD

** : $P < 0.01$ relative to control group

*** : $P < 0.001$ relative to control group

NS: non significant

4.2.2 Liver Function test

There was a significant difference in SGPT concentration in male and female patients relative to the male and female control groups at $p < 0.01$. However there was a significant increase in SGOT concentration in

male and female patients relative to the male and female control at $p < 0.01$. Also, there was a significant increase in ALK.Ph concentration in male and female patients relative to the male and female control at $p < 0.01$ (Table 4.2). There was a significant increase in total bilirubin concentration in male and female patients relative to the male and female control at $p < 0.01$. On the other hand, there was a significant increase in direct bilirubin concentration in male and female patients relative to the male and female control at $p < 0.01$. Moreover, there was no significant difference between the patients and control in the indirect bilirubin concentration at $p > 0.05$ (Table 4.2).

Table (4.2) : The liver function test , total bilirubin , direct bilirubin and indirect bilirubin concentrations in control and patients with CRF on hemodialysis according to sex difference .

The Biochemical test	Control group No. =63		CRF patients on Hemodialysis=63	
	Male	female	Male	Female
SGPT I.U	10.780±28.568	6.409±4.846	13.817±1.693 **	12.118±1.713 **
SGOT I.U	9.390±9.676	7.318±1.210	11.470±1.633 **	11.172±1.835 **
ALK.Ph I.U	32.024±6.820	30.454±6.898	73.048±66.078 **	62.818±69.975 **
Total Bilirubin μmol/L	7.077±0.643	7.027±0.731	9.928±2.007 **	9.431±1.433 **
Direct Bilirubin μmol/L	1.268±0.213	1.259±0.236	3.839±1.106 **	3.3.622±0.841 **
Indirect Bilirubin μmol/L	5.801±0.687	5.768±0.770	6.073±1.212 NS	6.049±0.855 NS

Values are mean $\pm$ SD

** : $P < 0.01$ relative to control group

NS: non significance .

4.2.3 LIPID Profiles

There was no significant difference in cholesterol concentration in male and female patients relative to the male and female control at $p > 0.05$. There was a significant increase in triglyceride concentration in male and female patients relative to the male and female control at $p < 0.01$ (Table 4.3). There was a significant increase in HDL concentration in male and female patients relative to the male and female control at $p < 0.05$. There was significant decrease in LDL concentration in male and female patients relative to the male and female control at $p < 0.01$. There was a significant decrease in vLDL in male and female patients relative to the male and female control at $p < 0.01$ (Table 4.3).

4.2.4 Serum Ions Concentration

There was no significant difference between the patients and control in serum sodium ($S.Na^+$) concentration at $p > 0.05$. There was a significant increase in serum Potassium ($S.K^+$) concentration in male and female patients relative to the male and female control at $p < 0.01$. There was no significant difference between the patients and control in serum calcium ($S.Ca^+$) concentration at $p > 0.05$ (Table 4-4). On the other hand there was a significant increase in serum phosphorus ($S.ph^+$) concentration male and female patients relative to the male and female control at $p < 0.01$. There was a significant decrease in serum copper concentration in male and female patients relative to the male

and female control at $p < 0.01$. There was a significant decrease in serum zinc concentration in male and female patients relative to the male and female control at $p < 0.01$ (Table 4-4).

Table (4.3) : The LIPID Profiles concentrations in controls and patients with CRF on hemodialysis according to sex difference .

The Biochemical test	Control group=63		CRF patients on Hemodialysis=63	
	Male	female	Male	female
Cholesterol mmol/L	3.814±0.663	3.550±0.704	3.856±1.382 NS	3.654±1.201 NS
Triglyceride mmol/L	1.095±0.372	1.022±0.330	2.143±1.118 **	2.027±1.362 **
HDL mmol/L	1.197±0.172	1.131±0.167	2.143±1.118 **	2.027±1.362 **
LDL mmol/L	3.165±0.204	3.150±0.232	2.413±1.199 **	2.677±1.303 **
VLDL mmol/L	0.729±0.084	0.709±0.092	0.423±0.225 **	0.396±0.278 **

Values are mean ±SD

** : $P < 0.01$ relative to control group

NS: non significant

Table (4.4) : The serum ions concentrations in controls and patients with CRF on hemodialysis according to sex difference .

The Biochemical test	Control group=63		CRF patients on Hemodialysis=63	
	Male	female	Male	female
Serum Ph ⁺ mmol/L	1.036±0.339	1.059±0.334	1.639±0.299 **	1.686±0.375 **
Serum Ca ⁺ mmol/L	2.224±0.228	2.213±0.281	2.178±0.550 NS	2.136±0.327 NS
Serum K ⁺ mmol/L	4.151±0.409	3.986±0.394	6.519±2.810 **	6.813± 1.701 **
Serum Na ⁺ mmol/L	139.975±6.198	141.136±7.213	138.850±10.527 NS	137.681±8.582 NS
Serum Cu µq/L	0.1700±0.018	0.1610±0.013	0.0700±0.005 **	0.0728±0.002 **
Serum Zn µq/L	0.0720±0.005	0.0710±0.0048	0.0202±0.005 **	0.0188±0.003 **

Values are mean ±SD

** : P<0.01 relative to control group

NS: non significant

4.2.5 Serum total Proteins , Serum Albumin ,Serum Globulin

There was a significant decrease in serum total protein concentration in male and female patients relative to the male and female control at p< 0.01(Table 4.5). There was a significant decrease in serum albumin concentration in male and female patients relative to the male and female control at p< 0.01. While there was a significant

difference in serum globulin concentration in male and female patients relative to the male and female control at $p < 0.01$ (Table 4.5).

Table (4.5) : The Serum total Proteins , Serum Albumin ,Serum Globulin concentrations in controls and patients with CRF on hemodialysis according to sex difference .

The Biochemical test	Control group=63		CRF patients on Hemodialysis=63	
	Male	female	Male	female
Serum total Proteins gm/L	70.460±5.294	69.818±5.095	62.249±15.111 **	60.772±16.503 **
Serum Albumin gm/L	41.333±4.095	40.454±4.171	26.312±4.910 **	20.363±3.836 **
Serum Globulin gm/L	29.254±2.923	29.318±3.014	36.936±13.817 **	40.409±16.025 **

Values are mean ±SD

** : $P < 0.01$ relative to control group.

4.3 The Hematological parameters Results

4.3.1 PCV ,Hb ,MCV ,MCHC , and MCH Count

There was a significant decrease in PCV concentration in male and female patients relative to the male and female control at $p < 0.01$. There was a significant decrease in Hb concentration in male and female patients relative to the male and female control at $p < 0.01$ (Table 4-6). There is a significant decrease in MCV concentration in male and female patients relative to the male and female control at $p < 0.05$ (Table 4-6). There was a significant decrease in MCHC concentration in male and

female patients relative to the male and female control at $p > 0.05$. There was a significant decrease in MCH concentration male and female patients relative to the male and female control at $p < 0.01$ (Table 4.6).

Table (4.6) : The PCV ,Hb ,MCV ,MCHC , and MCH Count

in controls and patients with CRF on hemodialysis according to sex difference.

The hematological test	Control group=63		CRF patients on Hemodialysis=63	
	Male	female	Male	female
Hb mg/dL	13.592±1.024	12.986±1.231	8.629±1.638 **	8.286±1.365 **
PCV L/L	41.243±3.112	39.363±3.632	25.439±5.215 **	24.272±4.025 **
MCHC gm/dL	33.740±1.633	33.700±0.158	30.390±9.67 **	30.049±1.220 **
MCH Pg	27.824±6.820	27.365±0.923	23.048±66.078 **	22.288±12.110 **
MCV fL	82.77±0.643	80.952±2.776	76.928±2.007 **	73.496±23.802 **

Values are mean ±SD

****** : $P < 0.01$ relative to control group

4.3.2 RBC Count, WBC Count, ESR, and Platelets Count

There was a significant decrease in RBC count in male and female patients relative to the male and female control at $p < 0.01$. There was a significant decrease in WBC count in male and female patients relative to the male and female control at $p < 0.01$ (Table 4.7). There was a significant increase in ESR concentration in male and female patients

relative to the male and female control at $p < 0.01$. There was a significant decrease in Platelets counts in male and female patients relative to the male and female control at $p < 0.01$ (Table 4.7).

Table (4.7) : The RBC Count, WBC Count, ESR, and Platelets Count in controls and patients with CRF on hemodialysis .

The hematological test	Control group		CRF patients on Hemodialysis	
	Male	female	Male	female
RBC $\times 10^9/L$	5.494 $\pm$ 0.312	4.045 $\pm$ 0.320	2.778 $\pm$ 0.684 **	2.822 $\pm$ 0.689 **
WBC $\times 10^9/L$	5.319 $\pm$ 0.948	5.195 $\pm$ 0.755	3.934 $\pm$ 2.254 **	4.536 $\pm$ 3.517 **
Platelets $\times 10^9/L$	332.948 $\pm$ 50.331	337.045 $\pm$ 51.701	214.538 $\pm$ 63.14 **	242.363 $\pm$ 87.213 **
ESR mm/hr	10.111 $\pm$ 3.501	9.181 $\pm$ 3.141	67.539 $\pm$ 37.582 **	72.181 $\pm$ 43.141 **

Values are mean $\pm$ SE

****** : $P < 0.01$ relative to control group

4.4. The biochemical and Hematological parameters of patients according to age groups .

4.4.1 The biochemical parameters of patients according to the age groups .

There was no significant difference in urea , createnine and uric acid concentrations among patients age groups . On the other hand, there was a significant difference in sugar concentrations at $p<0.05$ between 1st and 4th groups ,2nd and 4th groups,3rd and 4th groups,5th and 4th groups,6th and 4th group ,4th and 1st,2nd,3rd,5th,6th groups, table (4.8). There was a significant difference in SGPT concentrations at $p<0.05$ between 1st and 4th groups, 2nd and 4th groups , 3rd and 4th groups, 5th and 4th patients groups, 6th and 4th patient groups(4.2 ± 1.4), 4th and 1st, 2nd, 3rd, 5th, 6th groups ,table (4-8). There was a significant difference in SGOT concentrations ($p<0.05$) between 1st and 4th groups, 2nd and 4th groups, 3rd and 4th groups, 5th and 4th groups, 6th and 4th groups, 4th and 1st, 2nd, 3rd, 5th, 6th groups ,table (4-8).There was a significant difference in ALK.Ph concentrations at $p<0.05$ between 5th and 3rd groups, 6th and 3rd groups , 5th ,6th and 3rd patients groups , table (4-8).There was no significant difference in total bilirubine and direct bilirubine concentrations among patients age groups . On the other hand, there was a significant difference in indirect bilirubine concentrations at $p<0.05$ between 6th and 4th groups, 4th and 6th groups, table (4-8).There was no significant difference in total protein concentrations among patients age groups. While there was a significant difference in albumin concentrations at $p<0.05$ between the 2nd and 5th groups,3rd and 5th groups (27.9 ± 5.0) , 6th and 5th groups, there was a significant between the 2nd ,3rd ,6th , and 5th age groups ,table (4-8).There was a significant difference in globulin concentrations

at $p < 0.05$ between the 2nd and 4th age groups ,the 4th and 2nd age groups, table (4-8). There was no significant difference in cholesterol concentrations among patients age groups .On the other hand there was a significant difference in triglyceride concentrations at $p < 0.05$ between the 1st and 4th groups, the 3rd ,4th and 2nd age groups , the 3rd and 2nd groups, table (4-9) .There was a significant difference in HDL concentrations at $p < 0.05$ between 1st and 4th groups, the 3rd,4th and 2nd groups , the 3rd and 2nd groups, table (4-9). There was a significant difference in LDL concentrations at $p < 0.05$ between 1st and 6th groups. the 2nd and 6th groups , the 3rd and 6th groups , the 1st, 2nd ,3rd and 6th patients groups, table (4-9) .There was a significant difference in vLDL concentrations at $p < 0.05$ between 1st and 4th groups , the 2nd and 4th groups , the 1st ,2nd and 4th groups, table (4-9) .There was no significant difference in serum Na⁺, serum K⁺, and serum Ph⁺, Cu, and Zn concentration among patients age groups .On the other hand there was a significant difference in serum Ca⁺ concentrations at $p < 0.05$ between the 3rd and 6th groups , the 5th and 6th groups , the 3rd,5th and 6th patients groups, table (4-9) .

4.4.2 The Hematological parameters of patients according to the age groups.

There was a significant difference in RBC counts at $p < 0.05$ between the 1st and 4th groups , 5th and 4th groups , the 1st ,5th and 4th groups .There was no significant difference in ESR counts among patients groups , table (4-10).There was a significant difference in WBC counts at $p < 0.05$ between the 2nd ,3rdand 1st groups , the 2nd and 1st groups . the 3rd and 1st groups , table (4-10) There was a significant difference in Hb concentrations at $p < 0.05$ between the 2nd ,4th groups ,the 3rd and 4th groups , the 6th and 4th groups ,the 2nd,3rd,6th and 4th

groups, table (4-10) There was a significant difference in PCV concentrations at $p < 0.05$ between the 2nd, 4th groups, the 3rd and 4th groups, the 6th and 4th groups, the 2nd, 3rd, 6th and 4th patients age groups, table (4-10). There was a significant difference in MCHC concentrations at $p < 0.05$ between the 1st, 6th groups, the 2nd and 6th groups, the 6th and 3rd groups, the 4th and 6th groups, the 5th and 6th groups. the 1st, 2nd, 3rd, 4th, 5th and 6th patients groups, table (4-10). There was a significant difference in MCH concentrations at $p < 0.05$ between the 2nd, 5th groups, the 3rd and 5th groups, the 2nd, 3rd and 5th age groups, table (4-10). There was a significant difference in MCV concentrations at $p < 0.05$ between the 2nd, 3rd and 1st groups, the 2nd and 1st groups, the 3rd and 1st age groups, table (4-10). There was a significant difference in platelets concentrations at $p < 0.05$ between the 6th and 1st groups, the 5th and 6th groups, the 1st, 5th and 6th age groups, table (4-10).

Table (4.8): Some biochemical parameters concentrations in patients with CRF on hemodialysis according to age group

Biochemical parameters	Control No.63	1 st group	2 nd group	3 rd group	4 th group	5 th group	6 th group
Urea	3.5± 0.8	25.7± 12.5	36.3±13.195	31.6±21.9	30.5±12.3	27.2±12.3	31.3±14.7
Creatinine	66.7±6.4	441.8±234	389.1±218.1	489.7±207	432.5±180	507.5±204.7	333.0±201.1
Uric acid	211.4±36	255.5±33.5	260.4±31.6	263±33.4	267.6±33.5	257.4±33.5	260.4±31.6
Sugar	5.3±1.2	4.6±1.3* ⁵	5.5±1.1* ⁵	4.7±1.0* ⁵	7.0±2.2* ⁵	5.8±1.2* ^{1,2,3,4}	5.8±1.2
SGPT	9.2± 23.2	5.5±2.5* ⁴	8.1±7.0* ⁴	4.6±1.6* ⁴	33.2±62.4* ^{1,2,3,5,6}	6.1±4.2* ⁴	4.2±1.4 ⁴
SGOT	8.6± 7.8	7.1± 1.6* ⁴	7.9±1.5* ⁴	7.1±1.4* ⁴	18.0±20.3* ^{1,2,3,5,6}	7.4±1.6* ⁴	6.7±1.3* ⁴
ALK.Ph	31.4±6.8	80.0±90.7	68.8±41.5	115.4±89.5* ^{5,6}	79.6±47.6	61.2±40.1* ³	28.4±7.9* ³
Total Bilirubine	7.07± 0.64	9.6±3.3	9.7±1.1	9.9±1.3	9.6±1.4	9.7±1.4	10±1.9
Direct Bilirubine	1.268± 0.213	3.6±1.8	4.0±0.7	3.9±0.7	4.0±0.9	3.5±0.5	3.3±0.6
Indirect Bilirubine	5.8±0.6	6.0± 1.5	5.7± 0.4	5.9±0.7	5.5±0.9* ⁶	6.2±1.3	6.6±1.3* ⁴
total Proteins	70.4±5.2	59.7±9.3	55.3±7.1	64.8±16.5	67.7±22.3	59.7±16.4	69.1±14.3
Albumin	41.333±4.910	26.0±3.4	27.5±5.9* ⁵	27.9±5.0* ⁵	24.8±5.3	23.5±4.8* ^{2,3,6}	28.4±2.6* ⁵
Globulin	29.254±2.	33.6±8.3	27.8±2.9* ⁴	36.9±14.8	42.8±20.6* ²	36.2±14.3	40.7±15.6

Values are mean ±SE

* : P<0.05 relative to other age groups

Table (4.9): The lipid profile and serum ions in patients with CRF

Biochemical parameters	Control No.63	1 st group	2 nd group	3 rd group	4 th group	5 th group	6 th group
Cholesteol	3.8± 1.3	4.11± 1.00	3.43 ±1.01	3.93±1.47	3.40±2.23	3.76±1.14	4.82±0.48
Triglyceride	1.91±0.81	1.40±0.72 ^{*4}	2.28±1.32 ^{*34}	3.18±2.08 ²	2.17±0.76	1.86±1.08	2.10±1.19
HDL	1.17±0.17	1.91±0.81 ^{*4}	1.40±0.72 ^{*34}	2.28±1.32 ²	3.18±2.08 ^{*1,2}	2.17±0.76	1.86±1.08
LDL	3.16±0.21	2.44±0.78 ^{*6}	1.98±1.98 ^{*6}	2.42±1.45 ⁶	2.56±1.60	2.56±1.18	3.90±0.44 ^{* 1,2,3}
vLDL	0.72± 0.08	0.35±0.18 ^{*4}	0.28±0.14 ^{*4}	0.45±0.26	0.63±0.41 ^{*1,2}	0.43±0.15	0.37±0.21
Serum Na⁺	140.3± 6.5	141.09± 9.3	138.7±7.4	137.14±128	139±9.99	137±9.1	138.4±1.2
Serum K⁺	4.09±0.40	6.25±0.96	7.94±5.01	6.95±1.75	6.38±2.31	6.26±1.12	5.58±1.82
Serum Ca⁺	2.22± 0.24	2.20±0.27	2.20±0.35	2.05±0.33 ⁶	2.07±0.28	2.07±0.3 ^{*6}	2.54±1.09 ³⁵
Serum Ph⁺	1.04± 0.33	1.55±0.35	1.74±0.47	1.72±0.22	1.65±0.30	1.56±0.30	1.72±0.26
Serum copper	0.070±0.005	0.073±0.002	0.061±0.005	0.070±0.04	0.073±0.002	0.070±0.004	0.060±0.005
Serum zinc	0.020±0.005	0.018±0.003	0.016±0.005	0.018±0.03	0.017±0.002	0.020±0.005	0.016±0.005

Values are mean ±SE

* : P<0.05 relative to other age groups

Table (4.10):Shows the hematological parameters in patients with CRF on hemodialysis according to age groups.

The hematologic al test	Control No.63	1 st group	2 nd group	3 rd group	4 th group	5 th group	6 th group
RBC count	4.98±0.31	2.50±0.51 *4	2.75±0.47	2.84±0.70	3.33±0.91* ¹ ,5	2.71±0.62* 4	2.74±0.7 9
WBC count	5.27±0.88	5.91±4.7* ² ,3	3.18±1.69 *1	3.44±1.63 *1	4.23±2.35	4.40±2.41	3.55±1.9 8
Hb	13.73±1.0	8.72±1.82	7.82±1.39 *4	8.28±1.55 *4	9.86±1.31* ² ,3,6	8.76±1.01	7.57±1.5* 4
PCV	40.63±3.3	25.9±5.7	22.7±4.5* ⁴	23.9±4.7* ⁴	28.6±4.4* ^{2,3,6}	25.9±3.6	23.4±4.6* 4
MCHC	33.71±0.5	33.77±0.7 *6	34.11±1.8 *6	34.68±0.8 *6	34.59±1.9* ⁶	33.86±1.6* 6	31.36±04 *1,2,3,4,5
MCH	27.52±0.8	37.00±8.4	28.97±5.9 *5	30.12±6.4 *5	36.04±15.6	39.07±10. 9* ^{2,3}	31.11±11 .07
MCV	81.51± 2.34	108.80±24 .99* ^{2,3}	84.00±18. 63* ¹	86.88±18. 95* ¹	90.47±24.4 3	97.86±22. 73	96.48±33 .91
Platelets	327.8± 50.54	200.81±58 .18* ⁶	227.20±83 .82	235.07±81 .31	244.7±63.7 7	189.3±42. 56* ⁶	279.4±90 .15* ^{1,5}
ESR	10.11±3.5 0	66.5±22.6	67.5±37.5	58.4±37.5	63.6±24.6	67.5±33.5	55.4±22. 5

Values are mean ±SE

* : P<0.05 relative to other age

Discussion

5.1. History of the patients

5.1.1. Sex prevalence in CRF

It is revealed in this research that the males constitute 65% of patients with CRF on HD ,while the females constitute only 35% of the patients ,the male to female ratio was 1.8:1 . These results are in agreement with the studies done by **saxena et al .,(2001)** , **Al-Ghwery & Al-Asmari .,(2004)&Rahman et al.,(2005)** who concluded that the male to female ratio in their studies were 1.4:1, 2.14:1and 1.7:1 respectively . This high prevalence of CRF in males could be related to male habits like smoking and alcohol consumption. Also it is shown that the progression of CRF in males had a faster rate to end-stage renal failure than had women. In type 1 diabetes mellitus, there is an evidence that males are more likely to manifest signs of renal disease, such as proteinuria. The factors involved in this gender disparity may include diet, kidney and glomerular size, differences in glomerular hemodynamics, and the direct effects of sex hormones. In many, but not all, animal models of renal disease, estrogens slow the progression rate of renal diseases. Several studies have recently evaluated the effect of selective estrogen receptor modulators on renal function in humans (**Silbiger &Neugarten.,2008**) .

5.1.2. Age prevalence in CRF

In the present study the most higher incidence of CRF occurs in the 40s years of age. These results are in agreement with a study done in India by **saxena et al (2001)** who concluded that CRF was found to be more common between 40 s years of age .An other study done in Iceland by **Magnason et al (2002)** who concluded that CRF was found to be more

common between 50 s years of age. This could mean that the age prevalence of CRF may differ from one population to an other and it may be attributed to the nature of CRF in which, the signs and symptoms of CRF occurs gradually and do not become evident until the disease is far advanced because of the amazing compensatory ability of the kidneys **(Sarnak et al.,2005;Porth.,2007)** On the other hand most patients with CRF have a history of hypertension and DM which have along course of progression .The delay in the diagnosis and treatment; failure to recognize the symptoms and seriousness of these diseases remain a matter of major concern.

5.1.3. Blood groups prevalence in CRF

In the present study the higher incidence of CRF was found in blood group O+ve who constitute 43% of the patients on hemodialysis . These results may related to the prevalence of blood group O+ve in our population **(Skaik et al., 2007)** .

5.1.4. Smoking prevalence in CRF

In our study 58% of CRF patients were smokers and 42% of them were non smokers. These results are in agreement with a study done by **Ejerblad et al (2004)** which supports the hypothesis that smoking, particularly heavy smoking, contributes to the development of CRF as it has a systemic and local effects on the renal system. smoking is a preventable risk factor, identifying risk factors for CRF and preventing ESRD are critical because the dialysis population is expanding at a rate of 7% per year **(Ejerblad et al .,2004)**.

5.1.5. Chronic diseases prevalence in CRF

In the present research 52% of CRF patients on HD have history of HT .This finding is a well documented fact .**Simon.,(1990) Johnson et al/(1992)**

Agarwall et al., (2005) Rodicio & Alcazar.,(2007)and Ling et al.,2008 concluded that HT occurs in 80% to 90% of patients with renal insufficiency. Several factors contribute include expansion of ECF volume , Increased activity of the renin-angiotensin system , Dysfunction of the autonomic nervous system and diminished presence of vasodilators (**Ling et al.,2008**)

In the present research 36% of CRF patients on HD have history of DM .These results are in agreement with studies done by **Brenner et al.,1998) Bethesda.,(2007) and Karalliedde et al.,(2008)** who concluded that DM is the most common cause of CRF . Patients with DM are having not only a higher chance of developing renal failure ; but, they have more significant cardiovascular complications like HT , ischemic heart disease (**Li.,2001**). Adequate control of blood pressure with a variety of antihypertensive agents, including ACEIs, has been shown to delay the progression of albuminuria in both type 1 and type 2 diabetes. (**Brenner et al.,1998; Karalliedde et al.,2008**) . This indicate the complex relationship between HTand DM in the pathogenesis of CKD .

Ischemic heart diseases were present in 17% of CRF patients on HD .These results are in agreement with a study done by **Sarnak et al.,(2003) Kennedy et al.,(2003)Satyan et al.,(2007)** who concluded that CKD is associated with a markedly increased risk for cardiovascular disease, and the majority of deaths in ESRD are from cardiovascular causes . Anemia ,DM, and HT which are common in CKD are another risk factors for developing ischemic heart disease (**Jaradat & Molitoris.,2002**) .

5.2 the Biochemical parameter :

5.2.1 Blood urea ,creatinine ,uric acid and sugar .

This study shows that blood urea ,creatinine and uric acid concentrations increase in patients with CRF more than that in controls. These results are in agreement with previous studies done by **Lim et al.,(1995)** **Meyer & Hostetter.,(2007)**and **Kasper et al .,(2005)** . These studies concluded that urea and creatinine are quantitatively the most important solute excreted by the kidney and it was the first organic solute detected in the blood of patients with CRF . This increase in urea and creatinine level occurs because in CRF the kidney lose its ability to eliminate nitrogenous wastes from the blood results in accumulation of these substances in the blood (**Skorecki et al;2001,Porth .,2007**) . On the other hand, there was no significant difference in blood sugar between the patients and control subjects . These results disagreed with a study done by **Chen et al.,(2007)**. He concluded that high glucose level is associated with CKD and microalbuminuria due to metabolic syndrome . This controversy can be explained according to **Abe et al.,(2007)**. He explained that the concentration of blood glucose decrease during the passage of the plasma through the dialyzer and that in HD patients with diabetes, the glucose content of the HD solution plays an important role in preventing acute hypoglycemia and hyperglycemia during hemodialysis .

5.2.2 Liver Function test

The results show that the SGPT, SGOT, ALK.Ph, total bilirubine , direct bilirubine concentrations increased in patients with CRF more than that in controls. On the other hand ,there is no significant difference in indirect bilirubine concentrations between the patients with CRF and

controls .These results are in agreement with studies done by **Fuchs et al.,(1998)** and **Abo El yazeed et al.,(2006)** .

5.2.3 LIPID Profiles

The results shows that there is a significant increase in Triglyceride concentration and a significant decrease in HDL in patients with CRF . These findings are in agreement with a study done by **Vaziri.,(2005)**.In fact, serum TG are elevated in CKF due to an enhanced production of TG-rich lipoproteins such as vLDL by the liver ,in addition to dysfunction of TG degradation resulting from insufficient mitochondrial beta-oxidation of fatty acids(**Schaeffner et al.,2003**).There was a significant decrease in LDL concentration in the CRF patients. This finding disagrees with **Fried et al.,(2001)** who stated that LDL levels are often normal in patients with CRF. But however our results are in agreement with **mekki et al .,(2003)** and it could be related to a long term exposure to hemodialysis membrane .On the other hand there is no significant difference in Cholesterol concentrations between the patients with CRF and controls as it was recorded by **Vaziri.,(2005)**. He stated that plasma Cholesterol concentration is normal or even reduced in ESRD .Our results show a significant decrease in vLDL in CRF patients relative to the control . These results are in disagreement with a study done by **Schaeffner et al.,(2003)** who explained their results as there is enhanced production of TG-rich lipoproteins such as vLDL in the liver. This difference between our result and other research could be related to long term exposure to hemodialysis membrane .

5.2.4 Serum Ions Concentration

The present study shows that serum K^+ concentrations increase in patients with CRF as it was documented by **Gracia et al(2001) Rachoin & Weiberg .,(2008)** who concluded that there is sever increase in K^+ level in patients with CRF. The hyperkalemia is thought to result from the failure to follow dietary potassium restrictions and ingestion of medications that contain potassium, or from an endogenous release of potassium, as in case of trauma or infection (**Porth .,2007**). Hyperkalemia may also result from aldosterone inhibition secondary to decreased angiotensin (AngII) production (**Textor et al., 1982**). **Noman et al.,(2000)** agreed with the present study in that patients with CRF have a high level of Ph^+ , because the kidney is principally responsible for phosphate homeostasis. The kidneys regulates serum phosphate by modulating urinary phosphate excretion ,and this ability is lost in CRF (**Prie et al.,2002**). On the other hand there is no significant difference in Serum Na^+ concentrations between the patients with CRF and controls . These results are disagreed with a previous study done by **Williams.,2006** .He related that to a major inability of the kidney to response normally to change in Na^+ concentration .However, our result is in agreement with previous study done by **Biesen et al.,(2006)** .They explained normal level of serum Na^+ due to reduce Na^+ intake and humoral natriuretic factor in CRF which helps to increase sodium excretion and maintain normal Na^+ balance. In addition , we should not forget the effect of permanent hemodialysis on maintenance of normal Na^+ concentration. On the other hand salt wasting is a common problem in advanced renal failure because of impaired tubular reabsorption of sodium (**Porth .,2007**) which may support our results .

In relation to serum Ca^{+} level , the present results show that there is no significant difference in serum Ca^{+} concentration between CRF and controls in spite of the high level of Ph^{+} in patients under study. This is achieved by a routine administration of calcium supplements, with or without calcitriol for treatment of associated hypocalcaemia in CRF (**Kopple.,1999**). On the other hand, and in relation to serum copper and zinc, the results show a significant decrease in serum copper and zinc concentration in CRF patients relative to the controls . In fact ,this result runs homogeneously with a study done by **Kopple.,(1999)** and it is due to that the Patients with advanced CRF are at an increased risk for depletion of a number of minerals and nutrients including zinc and copper . This reduction in minerals that occur in CRF can be achieved by different ways. These ways may include Poor appetite due to abnormal taste sensation (**Ress & Shaw.,2007**) cytokines, and their roles in CRF, along with their effect on metabolic rate, (**Mak et al.,2005**), and acidosis and inflammation which are common in CRF(**Daschner et al.,1998**).

5.2.5 Serum total Proteins , Serum Albumin ,Serum Globulin

It is shown in this study, that Serum total protein , Serum albumin and globulin concentrations are decreased in patients with CRF relative to the controls .This hypoproteinemia may result from protein restriction ,anorexia , protein-energy malnutrition and chronic inflammation (**Kopple.,1999 ; Pierson., 2006 ; Porth., 2007**) .These results are in agreement with previous studies done by **Barton .,(2001) Prie et al., (2002) and Raj et al.,(2004)** .They concluded that cytokines such as IL-6 and $\text{TNF-}\alpha$ are known to induce muscle wasting .In addition, hemodialysis can result in cytokine-induced protein redistribution and net muscle protein loss .

5.3. The hematological studies.

5.3.1 prevalence of PCV & Hb in CRF

The present study shows a significant decrease in PCV and Hb concentration in patients group relative to the control .These results agreed with a previous studies done by **Tong & Nissenson .,(2001) Besarab & Levin .,(2000) & Jones et al.,(2005)** .These finding could explained as anemia first appears when the GFR falls below 40 ml/minute, and is present in most patients with ESRD because in renal failure, erythropoietin production usually is insufficient to stimulate adequate red blood cell production by the bone marrow .

5.3.2 Prevalence of MCV & MCH and MCHC in CRF.

There are significant decreases in MCV and MCH concentration in patients with CRF on HD,while there is no significant difference in MCHC concentration between controls and patients under the study. **Horl et al.,(2007)& Tinmouth et al.,(2008)** showed a similar results and explained that many persons on maintenance HD have hypochromic microcytic anemia .In addition to decrease erythropoietin production in CRF, many persons on maintenance HD also are iron deficient because of blood sampling and accidental loss of blood during dialysis(**Tinmouth et al.,2008**). Other causes of iron deficiency include factors such as anorexia and dietary restrictions that limit intake. In addition to its importance in erythropoiesis , Iron deficiency is the most common cause of hyporesponsiveness to erythropoiesis-stimulating agents (ESAs) in ESRD patients (**Horl et al.,2007**).

5.3.3 prevalence of RBC in CRF

From the results there is a significant decrease in RBC count in patients relative to the control .This can be explained due to inadequate erythropoietin production and accumulation of uremic toxins suppresses red cell production in the bone marrow of uremic patients and shorten their life span. (**Jones et al.,2005 and Horl et al.,2007**).

5.3.4 prevalence of WBC in CRF.

As reported by **Meuer et al. ,(1987)** ,our results show also a significant decrease in WBC count in patients with CRF on HD relative to the controls .This result can explained as that uremia is associated with various immune defects such as depressed peripheral lymphocyte count, impaired granulocyte phagocytic ability, monocytes dysfunction and T cell pre-activation, especially in HD patients who have repeated exposure of their blood to dialysis membranes .In addition , **Sarnak & Jaber .,(2000) U.S Renal Data System(2003) and Udayakumaret al.,(2006)** concluded that Severe scratching and repeated needle sticks, especially with HD, break the skin integrity and increase the risk for infection. After CVD, infections are the second most common cause of death in HD patients (**U .S Renal Data System2003**). Mortality risk due to sepsis is about 250-fold higher among HD patients than in the general population (**Sarnak &Jaber .,2000**) .

5.3.5 Prevalence of ESR in CRF

In this research there is a significant increase in ESR concentration in CRF patients relative to the control . The dialysis patients had a general

tendency for elevated ESR in the absence of malignancy or other clinical factors known to cause such levels. In uremic patients the mechanism of the elevated ESR is not fully explained and multiple factors such as: age, Hb level, hypocalcemia and elevated fibrinogen are probably involved. The possible correlation of the elevated ESR in dialysis patients is the chronic inflammatory response to the bioincompatible membranes (**Al-Homrany ,2002**).

5.3.6 Prevalence of Platelets in CRF

There is a significant decrease in Platelets counts in patients with CRF relative to the control. This finding is homogenous with **Abo El yazeed et al.,(2006)**. However our results may not go directly with the results of most studies, since they concluded that although platelet production is normal in ESRD but its function is impaired and that systemic anticoagulation that are generally used during HD interferes with plasmatic coagulation, platelet activation, or both. (**Remuzze et al.,1977, Eberst & Berkowitz ,1993 ; Joannidis& Oudemans-van.,2007**).

Conclusion and Suggestions for future work

Our study supports the hypothesis that CRF is a critical disease that results in a multi-systemic disorders. Therefore, patients who are at risk of CRF should be identified and treated. Any delay in the diagnosis and treatment; failure to recognize the symptoms and seriousness of CRF remain a matter of a major concern in our country. Creatinine clearance as well as the estimation of GFR should be performed routinely in all patients at risk. The renal disorders should be taken seriously and dealt with through a programmed health services at well equipped specialized clinics, and by a careful investigation. Furthermore, poor communication among staff in different specialties also adds to the difficulties of counseling the patients . The incidence of anemia and hypertension in this study was very high therefore, a good attention should be directed to study these problems and creates solutions for them . We were wish to measure the erythropoietin hormone level in patients with CRF .It is important for future work to study anemia in details and provide regular estimation of erythropoietin hormone and serum iron in all patients with CRF.



To

*My family
And
TO MY
HUSBEND AND CHILDREN*

*I dedicate this thesis with
love*

ASHEEL

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ASSEEL

Contents

Contents	Page
<i>Dedication</i>	I
<i>Acknowledgment</i>	II
<i>List of contents</i>	III-IX
<i>List of tables</i>	X
<i>List of figures</i>	XI
<i>List of abbreviations</i>	XII-XIV
<i>Abstract</i>	XV
Chapter One : Introduction	
<i>1.1 Introduction</i>	1-3
Chapter two : review of literature	
<i>2.1 Renal system</i>	4
<i>2.1.1 The kidneys</i>	4
<i>2.1.2 The ureters</i>	4
<i>2.1.3 The nephron</i>	5
<i>2.1.4 The bladder</i>	5
<i>2.1.5 The urethra</i>	6
<i>2.2 Renal failure</i>	6
<i>2.2.1 Acute renal failure</i>	6
<i>2.2.1.1 Pre renal failure</i>	7
<i>2.2.1.2 Intrinsic renal failure</i>	7

2.2.1.3 <i>Post renal failure</i>	8
2.2.1.4 <i>Assessment findings In renal failure</i>	8
2.2.2 <i>Chronic renal failure</i>	8
2.2.2.1 <i>Stages of CRF progression</i>	9
2.2.2.1.1 <i>Diminished renal reserve</i>	10
2.2.2.1.2 <i>Renal insufficiency</i>	11
2.2.2.1.3 <i>Renal failure</i>	11
2.2.2.1.4 <i>End stage renal disease</i>	11
2.2.2.2 <i>causes of CRF</i>	12
2.2.2.3 <i>Pathogenesis of CRF</i>	12
2.2.2.3.1 <i>Retained metabolic products</i>	12
2.2.2.3.1.1 <i>Over production of counter regulatory hormones</i>	13
2.2.2.3.1.2 <i>Under production of renal hormones</i>	14
2.2.2.3.2 <i>Cellular dysfunction in uremia</i>	14
2.2.2.3.4 <i>Pathophysiology</i>	15
2.2.2.3.4.1 <i>Intact nephron phenomenon</i>	15
2.2.2.3.4.2 <i>The magnification phenomenon</i>	15
2.2.2.3.4.3 <i>Trade-off hypothesis</i>	15
2.2.2.3.4.4 <i>Solutes handling in CRF</i>	15
2.2.2.3.4.4.1 <i>Creatinine and urea balance</i>	15
2.2.2.3.4.4.2 <i>Water balance</i>	16
2.2.2.3.4.4.3 <i>Sodium balance</i>	16

<i>2.2.2.3.4.4.4 Potassium balance</i>	<i>17</i>
<i>2.2.2.3.4.4.5 Hydrogen ion and acid-base balance</i>	<i>18</i>
<i>2.2.2.3.5 Progression of CRF</i>	<i>18</i>
<i>2.2.2.3.5.1 Intraglomerular hypertension and glomerular hypertrophy</i>	<i>18</i>
<i>2.2.2.3.5.2 Other secondary factors</i>	<i>19</i>
<i>2.2.2.3.5.2.1 Phosphate retention</i>	<i>19</i>
<i>2.2.2.3.5.2.2 Altered prostanoid metabolism</i>	<i>19</i>
<i>2.2.2.3.5.2.3 Dyslipidemia</i>	<i>19-20</i>
<i>2.2.2.3.5.2.4 Proteinuria</i>	<i>21</i>
<i>2.2.2.3.5.2.5 Tubulointerstitial disease</i>	<i>21</i>
<i>2.2.2.3.5.2.6 Retained toxins</i>	<i>21</i>
<i>2.2.2.3.5.2.7 Iron toxicity</i>	<i>21</i>
<i>2.2.2.3.6 Clinical manifestation of CRF</i>	<i>22</i>
<i>2.2.2.3.6.1 Neurological disorders</i>	<i>22</i>
<i>2.2.2.3.6.1.1 Disorders of neural functions</i>	<i>22</i>
<i>2.2.2.3.6.1.2 Psychological disorders</i>	<i>23</i>
<i>2.2.2.3.6.2 Hematological disorders</i>	<i>24</i>
<i>2.2.2.3.6.2.1 Anemia</i>	<i>24-25</i>
<i>2.2.2.3.6.2.2 Coagulopathies</i>	<i>25</i>
<i>2.2.2.3.6.3 Cardiovascular disorders</i>	<i>26</i>
<i>2.2.2.3.6.3.1 Hypertension</i>	<i>26</i>
<i>2.2.2.3.6.3.2 Heart diseases</i>	<i>27</i>

2.2.2.3.6.3.3 <i>Pericardaitis</i>	27
2.2.2.3.6.4 <i>Pulmonary disorders</i>	27
2.2.2.3.6.5 <i>Gastrointestinal disorders</i>	28
2.2.2.3.6.6 <i>Bone ,calcium ,phosphorus disorders</i>	28
2.2.2.3.6.6.1 <i>Minerals and bone disorders</i>	28-30
2.2.2.3.6.6.2 <i>Vitamin D metabolism</i>	30
2.2.2.3.6.6.3 <i>Phosphate metabolism</i>	30-31
2.2.2.3.6.6.4 <i>Calcium metabolism</i>	31
2.2.2.6.7. <i>Skin disorders</i>	32
2.2.2.6.8 <i>sexual dysfunctions</i>	32-33
2.2.2.6.9 <i>Altered immune functions</i>	33-34
2.2.2.6.10 <i>Metabolic syndrome</i>	34
2.2.2.4 <i>Management of CRF</i>	34-35
2.2.2.4.1 <i>Treatment of end stage renal failure</i>	36
2.2.2.4.1.1 <i>Hemodialysis</i>	36
2.2.2.4.1.2 <i>Peritoneal dialysis</i>	36
Chapter Three : Materials and Methods	
3.1 <i>Materials</i>	37
3.1.1 <i>Subjects of the study</i>	37
3.1.2 <i>Chemicals</i>	37
3.1.3 <i>Instruments</i>	37
3.2 <i>Methods</i>	39

3.2.1 Blood collection	39
3.2.2 Hematological studies	40
3.2.2.1 Red blood corpuscles counts	40
3.2.2.2 White blood cells counts	40
3.2.2.3 Determination of packed cell volume	41
3.2.2.4 Estimation of hemoglobin	41
3.2.2.5 Measurement of RBC indices	41
3.2.2.6 Determination of platelets count	42
3.2.2.7 Determination of erythrocytes sedimentation rate	42
3.2.3 The biochemical studies	42
3.2.3.1 Determination of random blood sugar	42
3.2.3.2 Determination of liver enzymes	42
3.2.3.3 Determination of serum bilirubine	43
3.2.3.4 Determination of non-protein nitrogen	43
3.2.3.5 Measurement of serum protein	44-45
3.2.3.6 Measurement of serum lipid	45-46
3.2.3.7 Measurement of serum ions	47-48
3.2.4 Statistical analysis	48
Chapter Four : Results	
4. Results	49
4.1 History of the patients	49
4.1.1 Sex differences in CRF	49

4.1.2 Age prevalence in CRF	50
4.1.3 Blood group prevalence in CRF	50
4.1.4 Smoking prevalence in CRF	51
4.1.5 Chronic disease prevalence in CRF	52
4.2 The biochemical parameters results according to sex differences	53
4.2.1 Blood urea ,sugar, createnine, and uric acid	53
4.2.2 Liver function test	54
4.2.3 Lipid profile	56
4.2.4 Serum ions concentrations	56
4.2.5 Serum total proteins ,albumin ,globulin	58
4.3 The hematological parameters results	59
4.3.1 PCV, Hb ,MCH, MCV, and MCHC counts	59
4.3.2 RBC ,WBC ,ESR ,and Platelets counts	60
4.4. The hematological and biochemical parameters of controls and patients according to age groups	62
4.4.1 The biochemical parameters of controls and patients according to age groups	62-63
4.4.2 The hematological parameters of controls and patients according to age groups	63-64
Chapter Five : Discussion and Conclusion	
5. Discussion	68
5.1 History of the patients	68
5.1.1 Sex prevalence in CRF	68
5.1.2 Age prevalence in CRF	68
5.1.3 Blood group prevalence in CRF	69

<i>5.1.4 Smoking prevalence in CRF</i>	<i>69</i>
<i>5.1.5 Chronic diseases prevalence in CRF</i>	<i>69-70</i>
<i>5.2. The biochemical parameters</i>	<i>70</i>
<i>5.2.1 Blood urea, creatinine ,uric acid ,and blood sugar</i>	<i>71</i>
<i>5.2.2 Liver function test</i>	<i>71-72</i>
<i>5.2.3 Lipid profile</i>	<i>72</i>
<i>5.2.4 Serum ions concentration</i>	<i>73-74</i>
<i>5.2.5 Serum total proteins ,albumin, globulin</i>	<i>74</i>
<i>5.3 The hematological studies</i>	<i>75</i>
<i>5.3.1 Prevalence of PCV and Hb in CRF</i>	<i>75</i>
<i>5.3.2 Prevalence of MCV,MCH and MCHC in CRF</i>	<i>75</i>
<i>5.3.3 Prevalence of RBC in CRF</i>	<i>76</i>
<i>5.3.4 Prevalence of WBC in CRF</i>	<i>76</i>
<i>5.3.5 Prevalence of ESR in CRF</i>	<i>76</i>
<i>5.3.6 Prevalence of platelets in CRF</i>	<i>77</i>
<i>Conclusion & suggestion for future work</i>	<i>78</i>
References	

LIST OF TABLES

Table No.	Title	Page
3-1	<i>Chemicals and materials used in the study</i>	38
3-2	<i>The main instruments used in the study</i>	39
4-1	<i>Urea ,creatinine ,uric acid and blood sugar in controls and patients with CRF according to sex difference</i>	54
4-2	<i>Liver function test in Controls and patients with CRF according to sex difference</i>	55
4-3	<i>Lipid profile in Controls and patients with CRF according to difference</i>	57
4-4	<i>Serum ions concentration in Controls and patients with CRF according to sex difference</i>	58
4-5	<i>Serum total protein, albumin ,globulin in controls and patients with CRF according to sex difference</i>	59
4-6	<i>PCV, Hb, MCV, MCH, MCHC count in controls and Patients with CRF according to sex difference</i>	60
4-7	<i>RBC, WBC, ESR and platelets count in controls and Patients with CRF according to sex difference</i>	61
4-8	<i>Serum urea, creatinine, uric acid, sugar, liver function test , serum proteins in CRF patients according to age groups</i>	65
4-9	<i>Lipid profile and serum ions in CRF according to age groups</i>	66
4-10	<i>The hematological parameters in patients with CRF on HD according to age groups</i>	67

LIST OF FIGURES

No. of figure	Title	Page
2-1	<i>Relation of renal function and nephron mass</i>	10
2-2	<i>The most common causes of chronic renal failure</i>	12
2-3	<i>The manifestations of chronic renal failure</i>	23
4-1	<i>Male to female ratio in patients with CRF</i>	49
4-2	<i>Age prevalence in patients with CRF</i>	50
4-3	<i>Blood groups distributions in patients with CRF</i>	51
4-4	<i>The ratio of smokers tonon-smokers in CRF patients</i>	52
4-5	<i>Chronic disease prevalence in patients with CRF</i>	53

LIST OF ABBREVIATIONS

<i>TNF-α</i>	<i>Tumor necrosis factor alpha</i>
<i>IL-1</i>	<i>Interleukin one</i>
<i>IL-6</i>	<i>Interleukin six</i>
<i>GFR</i>	<i>Glomerular filtration rate</i>
<i>CRF</i>	<i>Chronic renal failure</i>
<i>ESRD</i>	<i>End stage renal disease</i>
<i>ARF</i>	<i>Acute renal failure</i>
<i>BUN</i>	<i>Blood urea nitrogen</i>
<i>BNP</i>	<i>B type natriuretic peptide</i>
<i>NT-pro BNP</i>	<i>N-terminal pro BNP</i>
<i>HD</i>	<i>Hemodialysis</i>
<i>ATPase</i>	<i>Adenosine triphosphatase</i>
<i>RBC</i>	<i>Red blood cells</i>
<i>WBC</i>	<i>White blood cells</i>
<i>PTH</i>	<i>Parathyroid hormone</i>
<i>CrCl</i>	<i>Creatinine clearance</i>
<i>Na⁺</i>	<i>Sodium ion</i>
<i>K⁺</i>	<i>Potassium ion</i>
<i>ACEIs</i>	<i>Angiotensin converting enzyme inhibitors</i>

<i>Agn-II</i>	<i>Angiotensin II</i>
<i>Paco₂</i>	<i>CO₂ tension</i>
<i>HCO₃</i>	<i>Bicarbonate</i>
<i>TGF-β</i>	<i>Transforming growth factor</i>
<i>TGF-β1</i>	<i>Transforming growth factor 1</i>
<i>CKD</i>	<i>Chronic kidney disease</i>
<i>CVD</i>	<i>Cardiovascular disease</i>
<i>TG</i>	<i>Triglyceride</i>
<i>HDL</i>	<i>High density lipoprotein</i>
<i>LDL</i>	<i>Low density lipoprotein</i>
<i>vLDL</i>	<i>Very low density lipoprotein</i>
<i>BMI</i>	<i>Body mass index</i>
<i>ESAs</i>	<i>Erythropoiesis-stimulating agents</i>
<i>rhEPO</i>	<i>Recombinant human erythropoietin</i>
<i>LVH</i>	<i>Left ventricular hypertrophy</i>
<i>ROD</i>	<i>Renal osteodystrophy</i>
<i>ABD</i>	<i>Adynamic bone disease</i>
<i>b-MSH</i>	<i>Beta-melanocyte stimulating hormone</i>
<i>BP</i>	<i>Blood pressure</i>
<i>EDTA</i>	<i>Ethyl diamine tetra acetate</i>
<i>rpm</i>	<i>Round per minute</i>
<i>Hb</i>	<i>Hemoglobin</i>
<i>PCV</i>	<i>Packed cell volume</i>
<i>MCH</i>	<i>Mean corpuscle hemoglobin</i>
<i>MCV</i>	<i>Mean corpuscle volume</i>

<i>MCHC</i>	<i>Mean corpuscle hemoglobin concentration</i>
<i>ESR</i>	<i>Erythrocyte sedimentation rate</i>
<i>RBS</i>	<i>Random blood sugar</i>
<i>GOT</i>	<i>Glutamic oxaloacetic transaminase</i>
<i>POT</i>	<i>Glutamic pyruvic transaminase</i>
<i>ALK.Ph</i>	<i>Alkaline phosphatase</i>
<i>&</i>	<i>And</i>
<i>I.H.D</i>	<i>Ischemic heart disease</i>
<i>H.T</i>	<i>Hypertension</i>
<i>B.P.H</i>	<i>Benign prostatic hypertrophy</i>
<i>D.M</i>	<i>Diabetes mellitus</i>

Abstract

Background: *Chronic renal failure (CRF)* is a pathological syndrome developed due to a progressive destruction of renal structures by chronic nephropathies. It is characterized by a gradually increasing renal functions impairment. CRF can result from a number of conditions that cause permanent loss of nephrons, including chronic pyelonephritis, diabetic and non diabetic glomerulonephritis , hypertensive nephrosclerosis, , obstructive uropathies ,polycystic kidneys , drugs and toxins . Regardless of the cause, chronic renal failure results in the loss of renal cells with a progressive deterioration of glomerular filtration, tubular reabsorptive capacity, and endocrine functions of the kidneys.

Objective: This study is aimed to estimate variations in hematological and biochemical parameters in patients suffering from CRF on continuous hemodialysis aiming to prevent and treat these disorders .

Method: The patients were recruited from the artificial kidney unite at Marjan teaching hospital in Babylon city. They were suffering from chronic renal failure. Sixty three patients and sixty three healthy controls were enrolled in this study. Patients blood samples were used for the estimation of a number of biochemical and hematological parameters . The results of these patients were compared with that of the controls .

Results: The study reveals that there were significant increases in the concentrations of the following parameters in male and female patients with CRF relative to the controls . These parameters include blood urea ,creatinine ,uric acid ,SGOT, SGPT, ALK.Ph ,total bilirubine ,direct bilirubine, triglyceride ,HDL, serum Ph^+ , and serum K^+ concentrations.

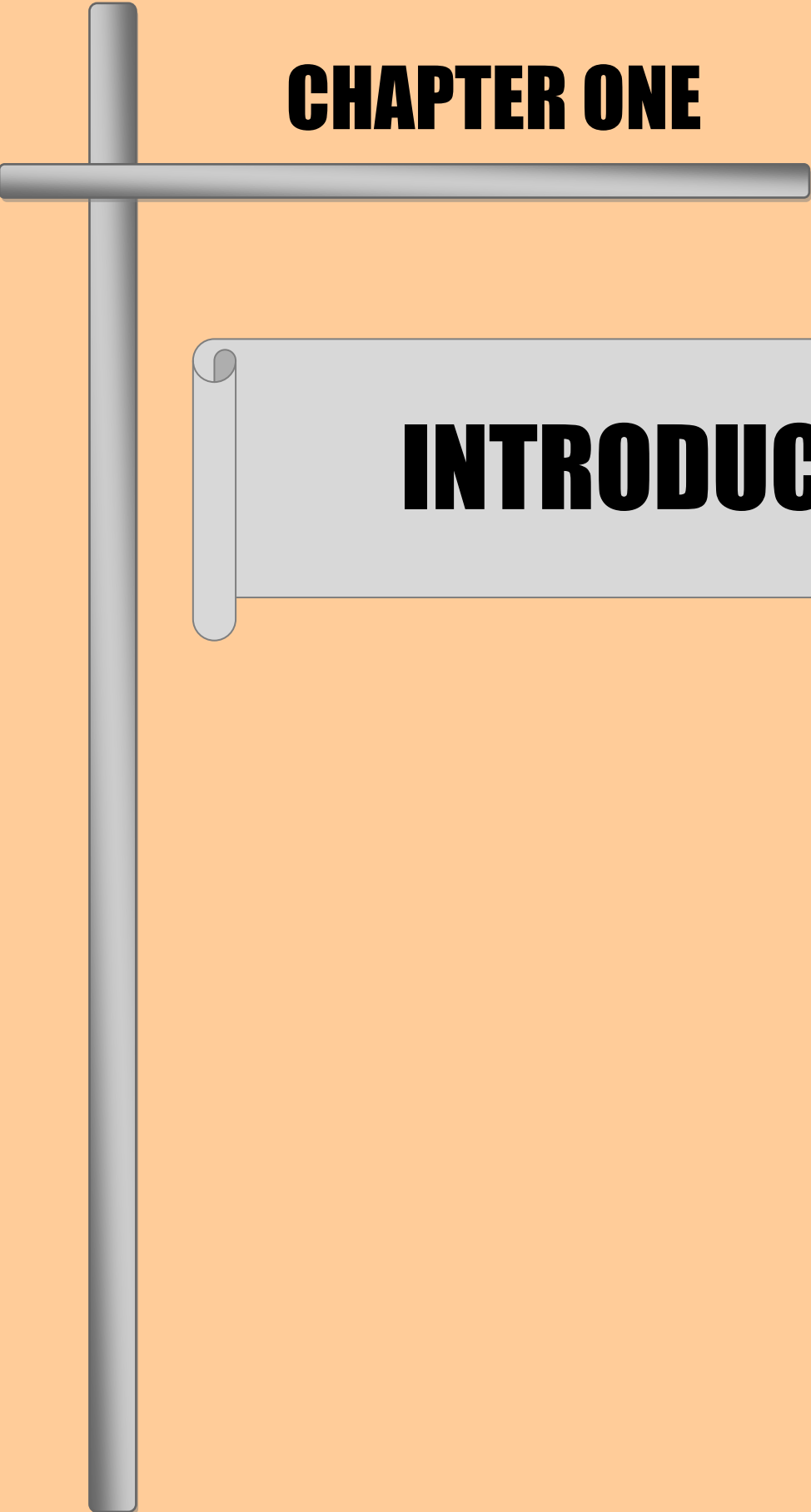
There were a significant decreases in the concentrations of the following parameters in male and female patients with CRF relative to the controls . These parameters include total serum protein ,serum albumin ,serum globulin ,LDL ,vLDL ,serum cu^+ ,and serum Zn^+ .

There were no significant differences in the concentrations of the following parameters in male and female patients with CRF relative to the controls. These parameters include blood sugar ,indirect bilirubine ,cholesterol , serum Na^+ , serum Ca^+ .

Conclusion: Our study supports the hypothesis that CRF is a critical disease that results in a multi-systemic disorders. Therefore, patients who are at risk of CRF should be identified and treated. Any delay in the diagnosis and treatment; failure to recognize the symptoms and seriousness of CRF remain a matter of a major concern in our country. Creatinine clearance as well as the estimation of GFR should be performed routinely in all patients at risk. The renal disorders should be taken seriously and dealt with through a programmed health services at well equipped specialized clinics, and by a careful investigation. Furthermore, poor communication among staff in different specialties also adds to the difficulties of counseling the patients . The incidence of anemia and hypertension in this study was very high therefore, a good attention should be directed to study these problems and creates solutions for them .

CHAPTER FIVE

DISCUSSION



CHAPTER ONE



INTRODUCTION



CHAPTER TWO



REVIEW OF LITERATURE

Materials & Methods

3.1 materials :

3.1.1 Subjects of study :

The study lasted from November/2007 to May/2008. Sixty three patients (22 females and 41 males) were included in the study. The number of each group ranged from 7-14 male and female .The patients were consist of sex groups and divided as follows: first group(21 to 30years),second group (31 to 40 years), third group(41 to 50 years),fourth group (51 to 60 years),fifth group(61 to 70 years), sixth group (over 70 years).

The patients were admitted to the artificial kidney unite at Marjan Teaching Hospital. They were suffering from chronic renal failure and clinically assessed by a specialist doctor. The control subjects consist of sex groups of apparently healthy subjects ,clinically assessed by a specialist doctor. Each group consists of 7-14 male and female . Their ages ranged as follows: first group(21 to 30 years),second group (31 to 40 years), third group(41 to 50 years),fourth group (51 to 60 years),fifth group(61 to 70 years), sixth group (over 70 years).

3.1.2 Chemicals :

The chemicals and materials used in this work and their sources are presented in table 3-1 .

3.1.3 Instruments :

The main instruments used in this work and their sources are presented in table 3-2.

Table 3-1 chemicals and materials used in the study

No.	Chemical materials	sources
2	Formal citrate solution	Crescent ,Saudi Arabia
3	Hydrochloric acid	Crescent ,Saudi Arabia
4	Glacial acetic acid	Crescent ,Saudi Arabia
5	Total protein kit	Human, Germany
6	Albumin kit	Human, Germany
7	Total cholesterol kit	Human, Germany
8	TG kit	Human, Germany
9	HDL kit	Biolab ,France .
10	Total calcium kit	Human, Germany
11	Potassium kit	Human, Germany
12	Sodium kit	Human, Germany
	Bilirubine kit	Human, Germany
13	Alkaline phosphatase kit	Biomeieux,France
14	SGOT kit	Randox ,UK
15	SGPT kit	Randox ,UK
	Glucose Kit	Human, Germany
17	Creatinine Kit	Human, Germany
	Phosphorus kit	Spinreact
	Uric acid kit	Biomerieux ,France
	Urea kit	Biomerieux , France
	HNO ₃	Sigma ,USA
	Ammonium Oxalate	Crescent ,Saudi Arabia

Table 3-2 The main instruments used in the study

No.	Instrument	sources
1	Hematocrit centrifuge	Hettich ,Germeny
2	Hemocytometer	Osaka , Japan
3	Light Microscope	Olympus , Japan
4	Water bath	Memmert, Germany .
5	Centrifuge	Universal , Germany
6	Hemoglobinometer	Optima, 202 , Japan
7	Spectrophotometer	Universal ,Germany
8	Plain tube	AFma – Dispo, Jordan
9	EDTA tube	AFma – Dispo, Jordan
11	Micro – pipette 100 -1000	Oxford ,USA
12	Micro – pipette 50 µl	Oxford ,USA
13	Disposal syringe	Asia medical instrument rotational
14	Microscope slide	Sail Brand ,China
15	Microscope Cover	Ataco, China
16	Refrigerator	Concord ,Lebanon
17	Ncubator	Memmert, Germany
18	Automated differential counter	Erma ,Japan
19	SpectrophotometerAA6200	Cecil ,Germany

3.2. Methods :

3.2.1 Blood collection:

The blood samples were in situ collected the artificial renal unite in Marjan teaching hospital .

The vein on the front of the elbow is almost employed for blood collection. The arm should be warm to improve blood circulation and

Chapter three. Materials & methods

distended the vein. A tourniquet was applied directly on the skin around the arm (usually from the left arm), approximately (6 – 8 cm) above the site of collection. The skin over the vein sterilized with a small pad of cotton wool soaked with 70% ethyl alcohol. Needles used were with 19 to 21 gauge. The site was dried with clean gauze, to prevent hemolysis by alcohol. Two groups of labeled tubes was used; the 1st tubes contain ethylene diamine tetra acetate (EDTA) as anti-coagulants to prevent clotting of blood to be used for hematological studies.

The second group of tubes were without anti-coagulant as plain tubes, for blood to be used for preparing sera for subsequent biochemical tests. The blood is allowed to clot for 45 minutes, sera were obtained and separated by centrifugation for 5 minutes at 5000 round per minute (rpm) and precautions were taken to avoid hemolysis. Each sample was labeled and given a serial number together with the patient name, the serum samples were frozen at (-20°C) for biochemical analysis (Bishop *et al.*, 2000).

3.2.2 . Hematological studies :

3.2.2.1 Red blood corpuscles count (RBCs count) :

Blood was diluted with formal citrate solution . The blood is drawn up to mark 0.5 in the RBCs pipette .The counting chamber (Neubaur hemocytometer) was used to count the RBCs(Dacie and Lewis, 2005).

RBC count = No. counted cells/ cubic mm x10,000

3.2.2.2 White blood cells count (WBCs count):

Blood is drawn in a clean and dry WBC pipette up to the mark 0.5 .The diluting fluid (Turk's solution) drawn up to mark 11 (dilution 1:20); the counting chamber a (Neubaur hemocytometer) was used to count the WBCs. (Dacia and lewis,2005):

WBC count /cubic mm of blood =No. of counted cells x 50 .

3.2.2.3 Determination of packed cells volume (PCV) :

Microhematocrit method was used to determine PCV.

Heparinized capillary tubes used, and blood was permitted to fill to approximately three quarters of their lengths (Dacie and Lewis, 2005) .

3.2.2.4 Estimation of hemoglobin (Hb) :

A cyanomethemoglobin method was used to estimate the hemoglobin contents of the blood. The method was based on Drabkins cyanide- ferric cyanide solution (Markarem,1974).

3.2.2.5 Measurement of RBCs indices :

i) The mean corpuscular volume (MCV) was calculated as the following :

$$\text{MCV} = \frac{\text{Packed cell volume}}{\text{Red corpuscles count } 10^{12}} \quad \text{Femtoliters (fL)}$$

ii) The mean corpuscular hemoglobin (MCH) was calculated as the following :

$$\text{MCH} = \frac{\text{Hemoglobin in g/dL}}{\text{RBCs count } 10^{12}} \quad = \text{picogram (pg)}$$

iii) The mean corpuscular hemoglobin concentration (MCHC) was calculated as following :

$$\text{MCHC} = \frac{\text{Hemoglobin gm/dL}}{\text{PCV}} \quad = \text{(in percent)}$$

(Dacia and Lewis,2005) .

3.2.2.6 Determination of Platelets counts

This is done by taking 0.38 ml of diluting fluid (1%ammonium oxalate to hydrolyze the RBCs,) and to which added 0.02 ml of blood taken by using hemoglobin pipette (Dacia and lewis,2005).

3.2.2.7 Determination of Erythrocytes sedimentation rate (ESR)

Sodium citrate solution in concentration of 0.25 (3.8 ml of sodium citrate +100 ml of distilled water) is added to 1ml of blood (Dacia and lewis,2005) .

3.2.3.The biochemical studies

3.2.3.1. Determination of Random Blood Sugar (RBS)

The glucose is determined after enzymatic oxidation in the presence of glucose oxidase. (according to procedure recommended by the Human, Germany).

3.2.3.2. determination OF Liver Enzymes

i) Determination of glutamic oxaloacetic transaminase (GOT):

Colorimetric method (Reitman and Frankel, 1957). Was used to measure the amount of oxaloacetic acid produced under fixed conditions. A reddish brown hydrazone formed when 2,4 dinitrophenyl hydrazine in alkaline solution, is added which can be measured by using spectrophotometer at 546 nm

ii) Glutamic pyruvic transaminase (GPT) determination :

Colorimetric method (Britman S.Frankel S., 1957) was used for the determination of GPT reaction with 2,4 dinitrophenyl hydrazine in

Chapter three. Materials & methods

alkaline solution, a brown colored hydrazones is formed which can be measured by using spectrophotometer at 505 nm .

iii) Determination of alkaline phosphatase (ALK.Ph) :

The method of kind and king was used to determine ALP and in which phenyl phosphate is hydrolyzed with the liberation of phenol and formation of phosphate. The amount of phenol which formed is estimated colorimetrically using spectronic 20 at 510 nm (Kind and King, 1954) .

3.2.3.3. Determination of Serum Bilirubine (total, direct and indirect)

i) Measurement of total serum bilirubine:

Working solution was prepared by mixing 20 volume R1 (sulfanilic acid, hydrochloric acid and dimethyl sulfoxide), with 1 volume R3 (sodium nitrate) . (Walter and Gerarde, 1970) .

ii) Measurement of direct serum Bilirubine :

Working solution was prepared by mixing 20 volume of reagent 2 (sulfanilic acid and hydrochloric acid) with 1 volume of reagent 3 (sodium nitrate) . (Walter and Gerarde, 1970) .

iii) Determination of indirect serum bilirubine :

It was obtained by the subtraction of the values of the direct bilirubine from the values of total bilirubine (Walter and Gerard,1970) .

3.2.3.4. Determination of Non-Protein Nitrogen.

i) Serum creatinine :

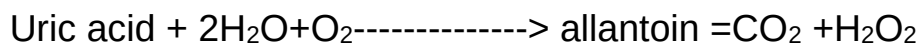
Reagent mixture was prepared by mixing 1ml picric acid with 1 ml sodium hydroxide. (Schirmeister,J.et al.,1964).

$$\text{Calculation} = 176.8 \times \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \quad (\mu\text{mol/L}).$$

ii) Serum uric acid :

Enzymatic determination of uric acid using the uricase-peroxidase-chromogen sequence:

uricase



(According to Mazieres B,1983.,Uric acid kit from bioMirox)

$$\text{concentration of the sample } \mu\text{mol/l} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times \text{standard concentration}$$

iii) Serum urea determination :

Working solution was prepared by mixing the content of one volume of reagent 2 (urease) to the bottle of reagent 3 (phosphate buffer sodium salicylate, sodium nitroprusside and EDTA (Fawcett and Scott,1960) .

3.2.3.5. Measurement of serum protein :

i)Measurement of total serum protein :

Cupric ions react with protein in alkaline solution to form a purpule complex . (Weichselbaum 1946,Josephson 1957).

$$\text{Calculation} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times 8 = \text{gm/dL}$$

ii) Determination of serum albumin :

Albumin in the presence of bormocresol green at slightly acid pH, produces a color change of the indicator from yellow - green to green blue. (according by albumin kit from spinreact) .

Absorbance of sample

Calculation =-----X concentration of standard

Absorbance of standard

=gm/dL concentration of albumin in the sample.

iii) Determination of serum globulin :

Serum globulin was determined by subtracting albumin from total serum protein and the results represented the values of serum globulin.(Bishop *et al.*, 2000) .

3.2.3.6.Measurement of Serum Lipids:

i) Determination of total serum cholesterol :

The cholesterol is determined after enzymatic hydrolysis and oxidation. The indicator quinoneimine is formed from hydrogen peroxide and 4-amino-antipyrine in the presence of phenol and peroxidase.

Optical density of sample

Calculation = -----X 200 = mg/dL

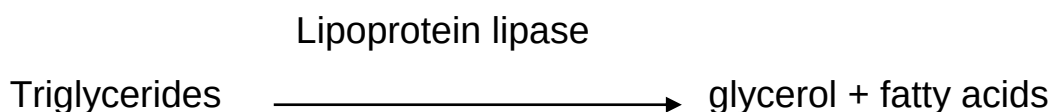
Optical density of standard

The solution were mixed and incubated for 5 minutes at 37°C.

(according to cholesterol kit from Biomagreb).

ii) Determination of triglycerides :

The triglycerides are enzymetically hydrolyzed to glycerol and fatty acids according to the following reaction:



$$\text{calculation} = \frac{\text{Optical density of sample}}{\text{Optical density of standard}} \times 200 = \text{mg/dL}$$

(according to triglycerides kit from Biomagreb) .

iii) Determination of HDL-Cholesterol

This reagent is only for treatment of specimens before determination of HDL-cholesterol with a reagent for total cholesterol. LDL ,vLDL and chylomicrons from specimens are precipitated by phosphtungstic acid (PTA) and Magnesium chloride. HDL-cholesterol obtained in supernatant after centrifugation is then measured with total cholesterol reagent(Biolab, france).

$$\text{Calculation} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times \text{standard concentration} \times 1.1$$

(mmol/L).

iv) Determination of LDL and v LDL –Cholesterol:

$$\text{LDL} = \text{Cholesterol} - (\text{HDL} + \text{v LDL}) = \text{mmol /L (Cecile .,2004)}$$

$$\text{V LDL} = \frac{\text{Triglyceride concentration}}{5} = \text{mmol/ L}$$

3.2.3.7.Mesurement of Serum Ions :

i) Determination of total calcium in serum samples :

Calcium in the sample, reacts with O-cresolphthaleine at alkaline pH (Barnett,R.N.,1973).

Absorbance of sample

Calculation = ----- X concentration of standard

Absorbance of standard

=mg/ dL concentration of calcium

ii) Determination of serum copper and zinc :

Atomic absorption spectrophotometer method was used to determine the trace elements(copper and zinc) in serum samples (Burits and Ashwood, 1999).

iii) Determination of potassium and sodium in serum

Potassium ions in a protein-free alkaline medium react with sodium tetraphenylboron to produce a finely turbid suspension of potassium tetraphenylboron. (According to Human ,Germany).

Sodium is precipitated with Mg-uranyl acetate ;the uranyl ions remaining in suspension form a yellow-brown complex with thioglycolic acid . According to (Human ,Germany).

iv)Determination of serum Phosphorus

Inorganic phosphorus reacts with molybdic acid forming a phosphomolybdic complex . Its subsequent reduction in alkaline medium originates a blue molybdenum.

Chapter three. Materials & methods

Calculation = Absorbance of sample/Absorbance of standard X
concentration of standard

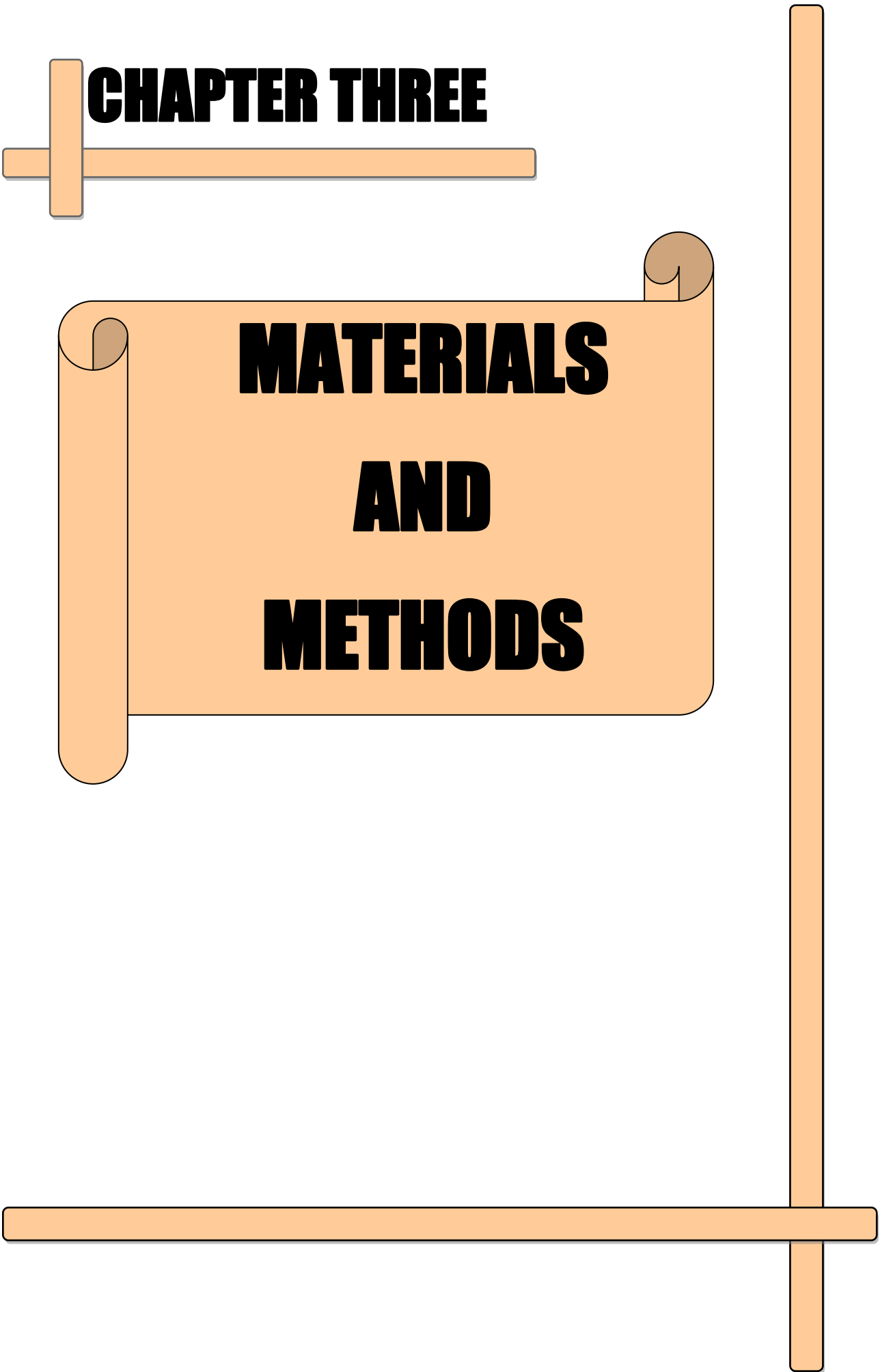
= mg\dl concentration of phosphorus in sample.

(According to phosphorus kit from spinreact).

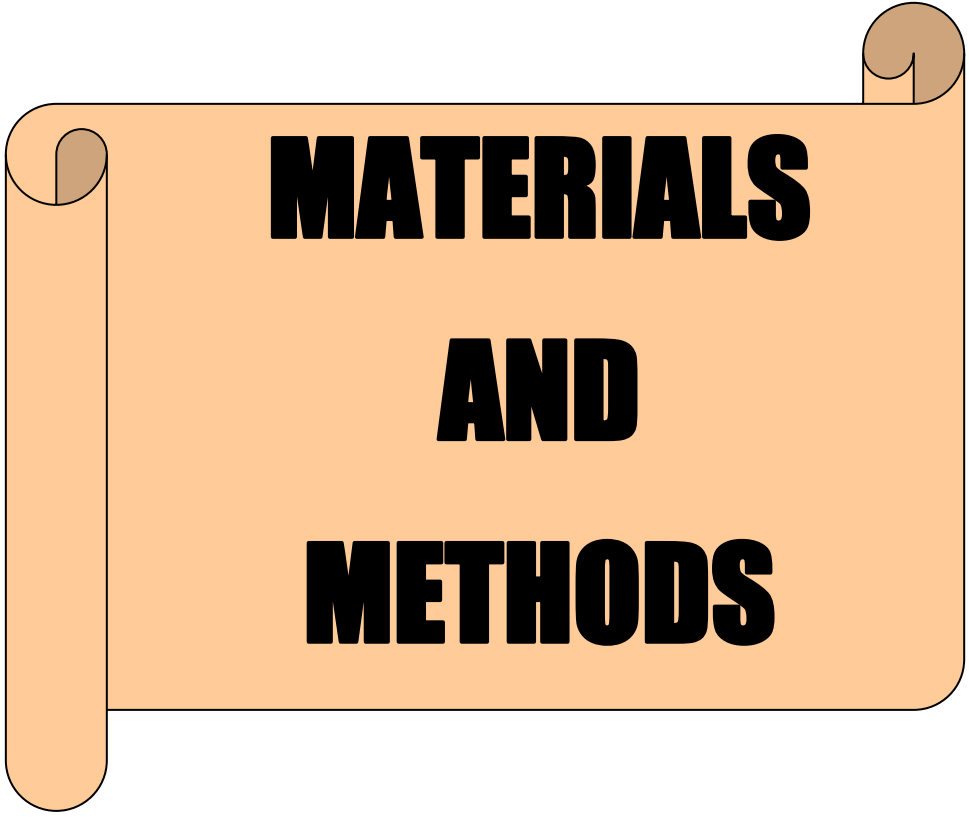
3.2.4 . Statistical analysis:

All values were expressed as means $\pm$ standard deviation (SD). The data were analyzed by using computerized SPSS program. Student's t-test was used to examine the differences between different groups and within groups .Firstly a comparisons between patients and control was done by using un paired t-test .

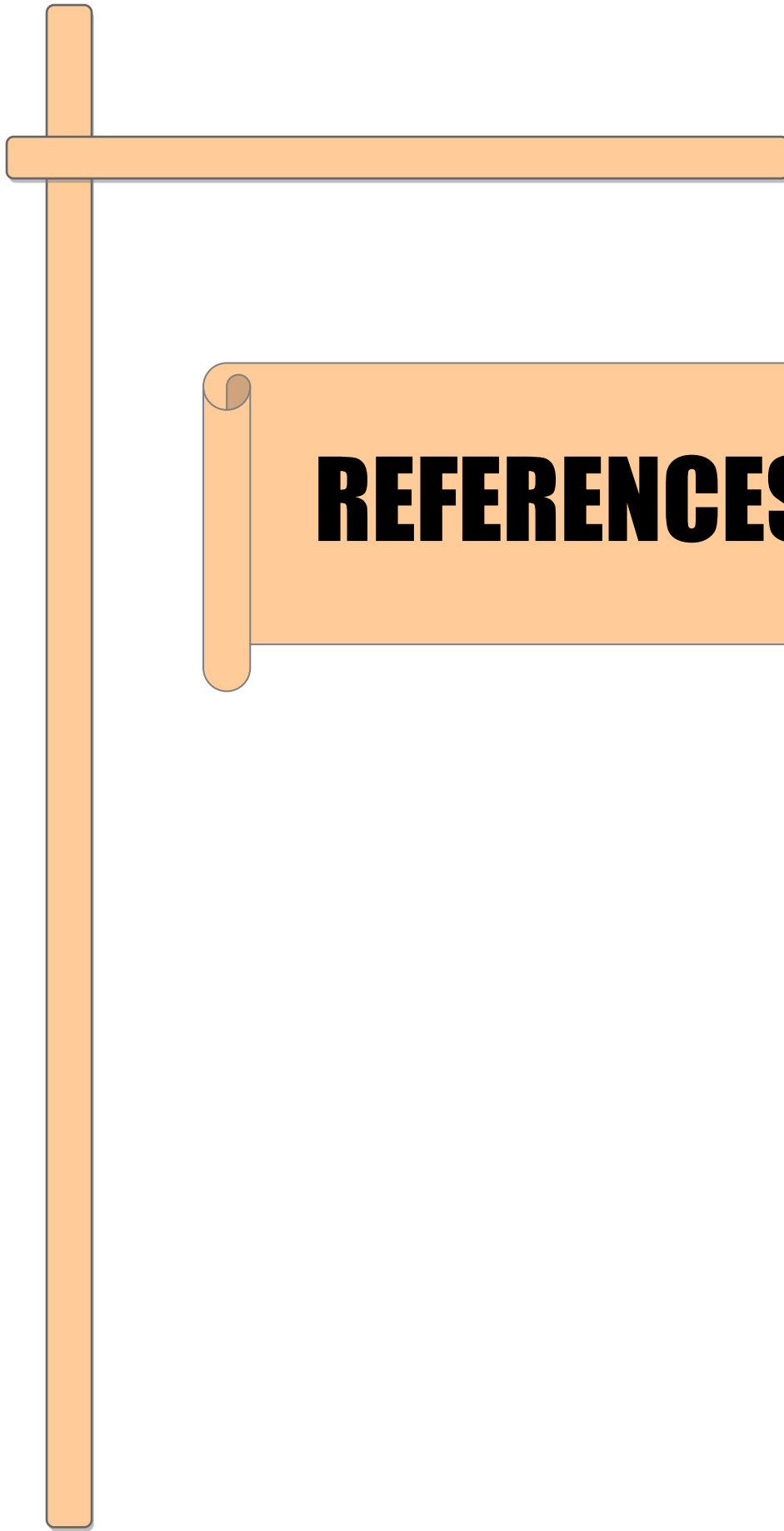
Comparison between and within patient groups were performed by using unpaired t-test and ANOVA test . A p value < 0.05 is considered to be statistically significant (Daniel, 1999).



CHAPTER THREE



MATERIALS AND METHODS



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CHAPTER FOUR

