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Assessment of Iron Profile among Sudanese Patients with Chronic Renal Failure in Shendi Town

A thesis Submitted for partial fulfillment of the Msc .Degree in Haematology

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Quran Verse

الآيـة

بسم الله الرحمن الرحيم

قال تعالى:

﴿ لَقَدْ أَرْسَلْنَا رُسُلَنَا بِالْبَيِّنَاتِ وَأَنزَلْنَا مَعَهُمُ الْكِتَابَ وَالْمِيزَانَ لِيَقُومَ النَّاسُ بِالْقِسْطِ وَأَنزَلْنَا الْحَدِيدَ فِيهِ بَأْسٌ شَدِيدٌ وَمَنَافِعُ لِلنَّاسِ وَلِيَعْلَمَ اللَّهُ مَن يَنصُرُهُ وَرُسُلَهُ بِالْغَيْبِ إِنَّ اللَّهَ قَوِيٌّ عَزِيزٌ ﴾

صدق الله العظيم

الآية 25 في سورة الحديد

الإهـــداء

إلى من ركع العطاء تحت قدميها

إلى الغالية التي لا نرى الأمل إلا من عينيها

أمي الحبيبة

إلي رمز الرجولة والتضحية

إلى من كلله الله بالهيبة والوقار

أبي الحبيب

إلى من شاركني حضن أمي ومنهم أستمد عزتي وإصراري

شقيقاتي وأشقائي الأحباء

إلى توائم روحي ورفيقات دربي صاحبات القلوب الطيبة والنوايا الصادقة

صديقاتي العزيزات

إلى من أنسني في دراستي وشاركني همومي

زميلاتي وزملائي الأعزاء

إلى الشموع التي ذابت لتنير كل شمعة في دربنا

أساتذتي الأجلاء

إلى جميع الأقارب والأصدقاء

شكر وعرفان

الحمد لله رب العالمين والصلاة والسلام على المبعوث رحمة للعالمين سيدنا محمد صلى الله عليه وسلم وعلى أله وصحبه أجمعين.

عملا بقوله تعالى :(وإذ تأذن ربك لئن شكرتم لأزيدنكم....) أشكر الله سبحانه وتعالى على نعمه التي لا تعد ولا تحصى ومنها توفيقه لإتمام هذا العمل وأتقدم بجزيل الشكر وخالص العرفان والتقدير إلى:

الدكتور: حمزة أحمد حسن

الذي شرفني بإشرافه على هذا العمل وعلى دعمه وتوجيهاته القيمة فجزاه الله خير الجزاء.

كما يسرني أن أقدم أسمى آيات الشكر والإمتنان إلى كل من دعمني وساندني في إجراء هذا البحث وأخص بالذكر الزميل أحمد محمد عثمان والزملاء طاقم التمريض بوحدة الغسيل الكلى بمستشفى المك نمر الجامعي.

والشكر والحمد لله من قبل وبعد .

Abstract

This is a descriptive cross-sectional case-control study conducted in Almek- Nimer University Hospital in Shendi town to evaluate iron profile in patients with chronic renal failure in the period of (March 2018 — July 2018).

The study included (30) patients who were diagnosed as chronic renal failure and the study group compared with (10) healthy volunteers as a control group.

Blood samples were collected from the two groups, Iron profile parameters were measured, Data was collected using a structured face to face questionnaire, and the (SPSS) version (11.5) program was used for data analysis.

The study revealed the patients with chronic renal failure were (73.3%) male and (26.6%) female, distributed as (66.7%) have (31-50) years old, (23.3%) have (51-70) years old ,and (10%) have (71-100) years old.

Iron profile indicated that the mean values of s.iron, s. ferritin and TIBC, were (182.2667ug/dL), (267.4000ug/L), and (195.2333ug/dL) respectively.

This study showed that chronic renal failure is responsible for significant changes in iron profile.

المستخلص

أجريت هذه الدراسة الوصفية المقطعية الحالة–الضابطة في مستشفي الملك نمر الجامعي بمدينة شندي لقياس مستوى معاملات الحديد لدى مرضى الفشل الكلوي المزمن في الفترة ما بين (مارس2018– يوليو 2018م). وكانت عينة الدراسة عبارة عن (30) مريض تم اختيارهم بصورة عشوائية. وقورنت نتائج الدراسة مع (10) متطوع سليم كمجموعة ضابطة.

تم جمع عينات الدم من جميع المرضي وتم تحليلها معمليا لإجراء فحص قياس معاملات الحديد. تم جمع المعلومات بواسطة الاستبيان ومن ثم استخدام برنامج الحزمة الإحصائية للعلوم الاجتماعية الذي يعرف ببرنامج (SPSS) لتحليل بيانات الدراسة.

أظهرت الدراسة أن المرضي (73.3٪) منهم ذكور و(26.7٪) منهم إناث وكانت أعمارهم من (31–50) سنة بنسبة (66.7%) و(51–70) بنسبة (23.3%) و(71–100) بنسبة (10%).

كما أظهرت الدراسة أن متوسط مستوى الحديد، الفرتين والسعة الارتباطية للحديد هو (182.2667ug/dL)، (267.4000ug/L)، (195.2333ug/dL) على التوالي.

وجدت الدراسة أن الفشل الكلوي المزمن مسئول عن تغيرات ذات دلالة مهمة تحدث في مستوى معاملات الحديد.

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BUN	Blood urea nitrogen
CAPD	Continuous ambulatory peritoneal analysis
CBC	Complete blood count
CERA	Continuous erythropoietin receptor activator
CHMP	Committee for human medical products
CKD	Chronic kidney disease
CRF	Chronic renal failure
CRF	C-Reactive protein
eGFR	Estimated glomerular filtration rate
EMA	The European medicine agency
EPO	Erythropoietin
ESAs	Erythropoietin –stimulating agents
ESRD	End stage renal disease
FDA	Food and drug administration
Fe^{3+}	Ferrous iron
GFR	Glomerular filtration rate
HAS	Health sciences authority
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HD	Hemodialysis
HIV	Human immunodeficiency virus
HLA	Human leucocytes antigen
HMW-ID	High molecular weight iron dextran
HSR	Hypersensitivity reaction
ID	Iron dextran
IV	Intravenous

LMW-ID	Low molecular weight iron dextran
NAT	Nucleic acid testing
ND	Non-dialysis
NHANES survey	National health and nutrition examination
NKF-KDOQI	National kidney foundation kidney disease outcomes quality
PD	Peritoneal dialysis
pmp	Per million of population
RBC	Red blood cell
RCT	Randomized control trails
rhEPO	Recombinant human erythropoietin
SC	Subcutaneous
SES	Socioeconomic status
TERA	Tranilast restenosis following angioplasty
TGA	Therapeutic good administration
TIBC	Total iron binding capacity
TM	Thalassemia major
TRALI	Transfusion - related lung injury
TSAT	Serum transferring saturation
UN	United kingdom
US	United state
USRDS	United states renal data system

1.1.Introduction

Chronic kidney disease (CKD) is an emerging global public health problem[1]. The conditions that replaced malnutrition and infection as leading causes of mortality during the 20th century [2] . Age-standardized death rates due to CKD have increased during the last 23 years. CKD has shifted from the 36th cause of death in 1990 to the 19th cause in 2013.[3] The worldwide increase in CKD and kidney failure necessitating renal replacement therapy and the high rate of cardiovascular mortality and morbidity attributable to CKD are poised to reach epidemic proportions over the next decade. CKD complications represent a considerable burden on global healthcare resources and only a small number of countries have sufficiently robust economies to meet the challenge posed by this disease. Socioeconomic differences in health exist and individuals of lower socioeconomic status (SES) have a higher risk for mortality and morbidity compared with those of higher SES[4] .A change in the global approach to CKD from the treatment of end stage renal disease (ESRD) to intensive primary and secondary prevention is therefore considered an absolute public health priority[5] .Africa is the second largest continent in the world, with a population of over 1 billion; 961.5 million people live in sub-Saharan Africa and 195 million in Northern Africa[6]. Africa now faces the dual challenge of infectious illnesses and chronic diseases. Africa's chronic disease burden is secondary to various factors, including increased life expectancy, changing lifestyle practices, poverty, urbanization and globalization [7] .The World Health Assembly advocated the Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013–2020. One of its targets is to reduce premature mortality from chronic diseases by 25% in 2025. These actions have the potential to make a significant impact on the burden of CKD.[8]

Unfortunately, CKD problem remains underestimated on the entire continent due to lack of epidemiological information from different African countries. There exists only a single systematic review conducted in sub-Saharan Africa, which concluded that CKD is a prevalent and potentially escalating disease across sub-Saharan Africa, with both communicable and non-communicable risk factors[9]. Strategies aimed at managing CKD epidemics in Africa critically depend on a reliable assessment of the burden of the problem and the establishment of affordable early detection programmes. Previous studies reported the prevalence of CKD among the general population or the specific prevalence of this condition in diseases that are recognized as drivers of renal damage (e.g. diabetes mellitus). These estimates have varied across studies due to differences in the methods of glomerular filtration rate (GFR) measurement, background risk (general population vs. high-risk groups) or demographic characteristics (e.g. age, gender).[10] In the UK, the incidence of ESRD has doubled over the last ten years and has now reached 101 patients per million of population (pmp)[11].This is below the European and US averages of approximately 135pmp and 336pmp, respectively[12]. Studies that have supplied data on the prevalence of CKD provide the opportunity to plan nephrology service requirements and develop stronger working relationships with the primary care teams in the community.

Studies such as the National Health And Nutrition Examination Survey (NHANES), which provided data on an adult unselected population, estimated that 4.7% of US adults had CKD stage 3 or higher (defined as an estimated glomerular filtration rate (eGFR) of <60ml/min/1.73m2). They also estimated that up to 11% of the general population (19.2 million) has some degree of CKD [13]. Similarly, a study of 112,215

patients registered with general practices in Greater Manchester, Kent and Surrey, UK, showed a prevalence of 4.9% [12,14].They also estimated that 5.9 million people may have stage 1 CKD with normal kidney function. In the Australian Diabetes, Obesity and Lifestyle (AusDiab) study of 10,949 patients, a prevalence of 11.2% of CKD stages 3–5 was found, but this does not provide an estimate for the general population .[15]

Renal diseases are associated with a variety of haemopoietic changes. Anemia parallels the degree of renal impairment and its most important cause is failure of renal erythropoietin secretion. Other factors include chronic blood loss, hemolysis and bone marrow suppression by retained uremic factors[16] .When kidneys are diseased or damaged, they do not make enough EPO. As a result, the bone marrow makes fewer red blood cells, causing anemia. When blood has fewer red blood cells, it deprives the body of the oxygen it needs. Other common causes of anemia in people with kidney disease include blood loss from haemodialysis and low levels of the nutrients in food such as iron, vitamin B12 and folic acid [17].

1.2.Rationale

Anemia is present in the majority of patients with chronic renal failure (CRF) on hemodialysis, The proximate cause of the anemia is an inadequate endogenous erythropoietin (EPO), iron is essential for hemoglobin formation and productive erythropoiesis, accurately assessing iron status is a prerequisite for diagnosing iron deficiency, monitoring the response to iron supplementation, and maintaining effective erythropoiesis in these patients.

1.3. Objectives

1.3.1. General objective:

-To measure iron profile among Sudanese patients with chronic renal failure.

1.3.2. Specific objectives:

-To measure serum iron in Sudanese patients with chronic renal failure.

-To measure serum ferritin in Sudanese patients with chronic renal failure.

-To measure total iron binding capacity (TIBC) in patients with chronic renal failure.

-To correlate iron profile in Sudanese patients with chronic renal failure with age, gender and duration of disease.

2.Literature Review

2.1.The kidneys:

2.1.1. The Kidney anatomy:

The kidneys are paired, bean-shaped organs located retroperitoneally on either side of the spinal column.

Macroscopically, a fibrous capsule of connective tissue encloses each kidney .when dissected longitudinally, two regions can clearly discerned an outer region called the cortex and an inner region called the medulla .

2.1.2. The kidney function:-

-Urine formation.

-Fluid and electrolyte balance.

-Regulation of acid base balance.

-Excretion of waste products of protein metabolism.

-Excretion of drugs and toxins.

-Secretion of hormones (renin, erythropoietin, 1,25-dihydroxy vitamin D_3 and prostaglandin)[18].

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 nonrenal origin.

2.2.1.Classification of renal failure:

Renal failure can occur as an acute or a chronic disorder. Acute renal failure is abrupt in onset and often is reversible if recognized early and

treated appropriately. In contrast, chronic renal failure is the end result of irreparable damage to the kidneys. It develops slowly, usually over the course of a number of years.

2.2.1.1.Acute renal failure:

Represents a rapid decline in renal function sufficient to increase blood levels of nitrogenous wastes and impair fluid and electrolyte balance. It is a common threat to seriously ill persons in intensive care units, with a mortality rate ranging from 42% to 88%.[19]

Although treatment methods such as dialysis and renal replacement methods are effective in correcting life-threatening fluid and electrolyte disorders, the mortality rate associated with acute renal failure has not changed substantially since the 1960 [20,21] .This probably is because acute renal failure is seen more often in older persons than before, and because it frequently is superimposed on other life-threatening conditions, such as trauma, shock, and sepsis. The most common indicator of acute renal failure is azotemia, an accumulation of nitrogenous wastes (urea nitrogen, uric acid, and creatinine) in the blood. In acute renal failure the glomerular filtration rate (GFR) is decreased. As a result, excretion of nitrogenous wastes is reduced and fluid and electrolyte balance cannot be maintained. Persons with acute renal failure often are asymptomatic, and the condition is diagnosed by observation of elevations in blood urea nitrogen (BUN) and creatinine.[21]

2.2.1.2. Chronic renal failure:

Unlike acute renal failure, chronic renal failure represents progressive and irreversible destruction of kidney structures. As recently as 1965, many patients with chronic renal failure progressed to the final stages of the disease and then died. The high mortality rate was associated with

limitations in the treatment of renal disease and with the tremendous cost of ongoing treatment. In 1972, federal support began for dialysis and transplantation through a Medicare entitlement program[22].Technologic advances in renal replacement therapy (i.e., dialysis therapy and transplantation) have improved the outcomes for persons with renal failure. In the United States, there are approximately 400,000 persons with end-stage renal disease who are living today, a product of continued research and advances in treatment methods [23] .Chronic renal failure can result from a number of conditions that cause permanent loss of nephrons, including diabetes, hypertension, glomerulonephritis, and polycystic kidney disease. Typically, the signs and symptoms of renal failure occur gradually and do not become evident until the disease is far advanced. This is because of the amazing compensatory ability of the kidneys. As kidney structures are destroyed, the remaining nephrons undergo structural and functional hypertrophy, each increasing its function as a means of compensating for those that have been lost .It is only when the few remaining nephrons are destroyed that the manifestations of renal failure become evident. Regardless of cause, chronic renal failure results in progressive deterioration of glomerular filtration, tubular reabsorptive capacity, and endocrine functions of the kidneys. All forms of renal failure are characterized by a reduction in the GFR, reflecting a corresponding reduction in the number of functional nephrons.

2.2.1.2.1.Stages of Progression of chronic renal failure:

The rate of nephron destruction differs from case to case, ranging from several months to many years. The progression of chronic renal failure usually occurs in four stages: diminished renal reserve, renal insufficiency, renal failure, and end-stage renal disease.[24]

2.2.2.Cliniical Manifestations of renal failure:

The clinical manifestations of renal failure include alterations in water, electrolyte, 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 Uremia, which literally means "urine in the blood," is the term used to describe the clinical manifestations of ESRD. Uremia differs from azotemia, which merely indicates the accumulation of nitrogenous wastes in the blood and can occur without symptoms. There currently are four target populations that comprise the entire population of persons with chronic renal failure: persons with chronic renal insufficiency, those with ESRD being treated with hemodialysis, those being treated with peritoneal dialysis, and renal transplant recipients. The manifestations of renal failure are determined largely by the extent of renal function that is present (e.g., renal insufficiency, ESRD), coexisting disease conditions, and the type of renal replacement therapy the person is receiving.[25]

2.2.3. Hematological disorders in renal failure:

Chronic anemia is the most profound hematologic alteration that accompanies renal failure. Anemia first appears when the GFR falls below 40 mL/minute and is present in most persons with ESRD. Several factors contribute to anemia in persons with chronic renal failure, including a erythropoietin deficiency, uremic toxins, and iron deficiency. The kidneys are the primary site for the production of the hormone erythropoietin, which controls red blood cell production. The accumulation of uremic toxins further suppresses red cell production in the bone marrow, and the cells that are produced have a shortened life span. Iron is essential for erythropoiesis. Many persons receiving

maintenance hemodialysis also are iron deficient because of blood sampling and accidental loss of blood during dialysis. Other causes of iron deficiency include factors such as anorexia and dietary restrictions that limit intake. When untreated, anemia causes or contributes to weakness, fatigue, depression, insomnia, and decreased cognitive function. There is also increasing concern regarding the physiologic effects of anemia on cardiovascular function. The anemia of renal failure produces a decrease in blood viscosity and a compensatory increase in heart rate. The decreased blood viscosity also exacerbates peripheral vasodilatation and contributes to decreased vascular resistance. Cardiac output increases in a compensatory fashion to maintain tissue perfusion. Echocardiographic studies after initiation of chronic dialysis have shown ventricular dilatation with compensatory left ventricular hypertrophy.[26] Anemia also limits myocardial oxygen supply, particularly in persons with coronary heart disease, leading to angina pectoris and other ischemic events[27] .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. A remarkable advance in medical management of anemia in persons with ESRD occurred with the availability of recombinant human erythropoietin (rhEPO). Secondary benefits of treating anemia with rhEPO, previously attributed to the correction of uremia, include improvement in appetite, energy level, sexual function, skin color, and hair and nail growth, and reduced cold intolerance. Frequent measurements of hematocrit are necessary. Worsening hypertension and seizures have occurred when the hematocrit was raised too suddenly. Because iron deficiency is common among persons with chronic renal failure, iron supplementation often is needed. Iron can be given orally or intravenously. Intravenous iron may be used for treatment of persons who

are not able to maintain adequate iron status with oral iron. Bleeding disorders, which are manifested by epistaxis, menorrhagia, gastrointestinal bleeding, and bruising of the skin and subcutaneous tissues, are also common among persons with chronic renal failure. Although platelet production often is normal in ESRD, platelet function is impaired. Platelet function improves with dialysis but does not completely normalize, suggesting that uremia contributes to the problem. Anemia may accentuate the problem by changing the position of the platelets with respect to the vessel wall. Normally the red cells occupy the center of the bloodstream, and the platelets are in the skimming layer along the endothelial surface. In anemia, the platelets become dispersed, impairing the plateletendothelial cell adherence needed to initiate hemostasis .[28]

2.2.4. Diagnosis and evaluation of anemia in CKD:

Anemia is an initial laboratory sign of an underlying clinical problem in patients with or without CKD, for which is necessary a complete blood count, that include total RBC count, Ht, and Hb concentration. In patients with CKD but stable kidney function, the onset or the progression of anemia may predict a new clinical problem which could be the expression of a blood loss or interference with red cell production. For this reason, anemia should be evaluated independently of CKD stage in order to identify any reversible process contributing to the anemia. There is a large list of causes and approaches to the diagnosis that can be found in a standard textbook of medicine or hematology useful for the clinical general practitioner. However, the causes of acquired anemia are myriad and too many to follow all steps of internistic guideline. A comprehensive list of this causes and diagnostic approach is desirable for CKD patients. The most commonly encountered reversible cause of worsening anemia

in CKD patients, other than anemia directly related to CKD, is iron deficiency. CKD patients show a gradual decrease in Hb levels that usually is related to the decline in the GFR, suggesting the need for regular monitoring Hb concentration. As renal function declines in patients with more advanced CKD stages, the incidence and prevalence of anemia increases. Therefore, in order to identify CKD patients at high risk for therapeutic intervention, Hb concentration monitoring should be more frequent in proportion to CKD stages.

The frequency of Hb monitoring, regardless of CKD stage, should be influenced by both Hb level and rate of decline in Hb level. Monthly monitoring of Hb concentration is recommended in patients undergoing dialysis replacement therapy (HD hemodialysis or PD: peritoneal dialysis). It is important to remember that for HD patients Hb monitoring is traditionally performed prior to a midweek HD session, while this is not essential in PD patients. As in all patients, Hb testing should be performed whenever clinically indicated, such as after a major surgical procedure, hospitalization, or bleeding episode. Initial evaluation of the anemia in CKD, regardless of age and CKD stage, shoud include the following tests: Complete blood count (CBC), that should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count; Absolute reticulocyte count; Serum ferritin level; Serum transferrin saturation (TSAT); Serum vitamin B12 and folate.[29]

2.2.5.Treatment of renal failure:

During the past several decades, an increasing number of persons have required renal replacement therapy with dialysis or transplantation. The growing volume is largely attributable to the improvement in treatment and more liberal policies regarding who is treated. Between 1980 and 1992, there was a twofold reported increase in treatment for ESRD[30] . In

1998, almost 245,910 persons were receiving dialysis therapy in the United States, and another 13,272 underwent kidney transplantation.[31]

2.2.5.1.Medical management:

Chronic renal failure can be treated by conservative management of renal insufficiency and by renal replacement therapy with dialysis or transplantation. Conservative treatment consists of measures to prevent or retard deterioration in remaining renal function and to assist the body in compensating for the existing impairment. Interventions that have been shown to significantly retard the progression of chronic renal insufficiency include dietary protein restriction and blood pressure normalization. Various interventions are used to compensate for reduced renal function and correct the resulting anemia, hypocalcemia, and acidosis. These interventions often are used in conjunction with dialysis therapy for patients with ESRD.

2.2.5.2.Dialysis and transplantation:

Dialysis or renal replacement therapy is indicated when advanced uremia or serious electrolyte imbalances are present. The choice between dialysis and transplantation is dictated by age, related health problems, donor availability, and personal preference. Although transplantation often is the treatment preference, dialysis plays a critical role as a treatment method for ESRD. It is life sustaining for persons who are not candidates for transplantation or who are awaiting transplantation. There are two broad categories of dialysis: hemodialysis and peritoneal dialysis.

2.2.5.2.1.Hemodialysis:

The basic principles of hemodialysis have remained unchanged throughout the years, although new technology has improved the efficiency and speed of dialysis[32].A hemodialysis system, or artificial kidney, consists of three parts:

a blood compartment, a dialysis fluid compartment, and a cellophane membrane that separates the two compartments. The cellophane membrane is semipermeable, permitting all molecules except blood cells and plasma proteins to move freely in both directions—from the blood into the dialyzing solution and from the dialyzing solution into the blood. The direction of flow is determined by the concentration of the substances contained in the two solutions. The waste products and excess electrolytes in the blood normally diffuse into the dialyzing solution. If there is a need to replace or add substances, such as bicarbonate, to the blood, these can be added to the dialyzing solution .During dialysis, blood moves from an artery through the tubing and blood chamber in the dialysis machine and then back into the body through a vein. Access to the vascular system is accomplished through an external arteriovenous shunt (i.e., tubing implanted into an artery and a vein) or, more commonly, through an internal arteriovenous fistula (i.e., anastomosis of a vein to an artery, usually in the forearm). Heparin is used to prevent clotting during the dialysis treatment; it can be administered continuously or intermittently.

2.2.5.2.2. Peritoneal dialysis:

Peritoneal dialysis uses the same principles of diffusion, osmosis, and ultrafiltration that apply to hemodialysis. The thin serous membrane of the peritoneal cavity serves as the dialyzing membrane. A silastic catheter

is surgically implanted in the peritoneal cavity below the umbilicus to provide access. The catheter is tunneled through subcutaneous tissue and exits on the side of the abdomen .The dialysis process involves instilling a sterile dialyzing solution (usually 2 L) through the catheter during a period of approximately 10 minutes. The solution then is allowed to remain, or dwell, in the peritoneal cavity for a prescribed amount of time, during which the metabolic endproducts and extracellular fluid diffuse into the dialysis solution. At the end of the dwell time, the dialysis fluid is drained out of the peritoneal cavity by gravity into a sterile bag. Glucose in the dialysis solution accounts for water removal. Commercial dialysis solution is available in 1.5%, 2.5%, and 4.25% dextrose concentrations. Solutions with higher dextrose levels increase osmosis, causing more fluid to be removed. The most common method is continuous ambulatory peritoneal dialysis (CAPD), a self-care procedure in which the person manages the dialysis procedure and the type of solution (i.e., dextrose concentration) used at home.

2.2.5.2.3.Transplantation:

Greatly improved success rates have made kidney transplantation the treatment of choice for many patients with chronic renal failure. The availability of donor organs continues to limit the number of transplantations performed each year. Donor organs are obtained from cadavers and living related donors (e.g., parent, sibling). The success of transplantation depends primarily on the degree of histocompatibility, adequate organ preservation, and immunologic management.[33]

2.3.Red cells transfusion to treat anemia in CKD:

in CKD After the addition of ESAs to available treatments for anemia in CKD patients, there has been a marked decline in

transfusion events in this population. Current anemia management guidelines recommend reaching the Hb target using the lowest possible ESA dosages to avoid the need for red blood cell transfusions[34]. Although transfusions provide a rapid primary benefits of maintaining a sufficient oxygen carrying capacity improving anemia-related symptoms, and are considerably safer than in the past, transfusion-related risks persist. Risks associated with blood transfusion include transfusion errors, volume and iron overload, hyperkalemia, citrate toxicity (leading to metabolic alkalosis and hypocalcemia), hypothermia, coagulopathy and immunologically-mediated transfusion reactions, all of which are uncommon. The most significant current risk of mortality from blood transfusion due to administrative error results in hemolysis (one in 60,000) and death (one in 600,000) [35].The development of antibodies to human leukocytes antigen (HLA), can affect a patient's ability to receive organ transplants[36].The risk of HLA sensitization after blood transfusion has changed over time probably, at least in part, due to changes in blood transfusion practices and the use of more precise methods to measure allosensitization. HLA sensitization was associated with several factors such as previous pregnancies and previous transplantation. Available data suggest that men have a much lower risk of HLA sensitization following transfusion than women, and women with multiple pregnancies have a much greater risk of HLA sensitization than nulliparous women. However, more recent data from the US Renal Data System (USRDS) 2010 Annual Report[37]have challenged this assumption, suggesting that males receiving previous blood transfusions may also be at increased risk. One of the most easily identifiable cause of transfusion-related morbidity

and mortality in the United States is the transfusion-related acute lung injury (TRALI)[38] .However, because of the varied criteria used to diagnose this syndrome, the true incidence is not known. Estimated incidence of TRALI is 8 cases per 100000 units of blood components transfused. Risk factors for TRALI are age and illness severity, and the risk for development of TRALI increases with the number of units transfused. TRALI is characterized by pulmonary edema, hypoxemia, respiratory distress, and radiographic evidence of new bilateral pulmonary infiltrates occurring within minutes to 6 hours after transfusion. Fever, tachycardia, cyanosis, hypotension, and frothy sputum may also be present. Risks of transfusion transmitted viral infections are extremely low, currently estimated to be approximately one in 1.4 x 106 to 2.4 x 106 units for human immunodeficiency virus (HIV), one in 872,000 to 1.7 x 106 for hepatitis C virus (HCV), and one in 58,000 to 149,000 for hepatitis B virus (HBV) [39]. Rigorous predonation screening has led to a rapid decline in prevalence of HIV and HCV in first time blood donors, with HIV decreasing from 0.03% (1991-1992) to 0.02% (1993-1996) and HCV decreasing from 0.63% (1992) to 0.40% (1996), despite an increase in prevalence in the general population for both HIV (0.3% in 1992) and HCV (1.8% in 1988-1994) .[40]

introduction of nucleic acid amplification testing (NAT) for HIV and HCV in 1999, further reduced the window period between a potential blood donor infection and detectability by screening tests at time of donation. [41]

2.4.Iron status in CKD:

Adequate iron stores are essential to optimize the effects of ESA, such as recombinant human erythropoietin (EPO) or darbepoietin alfa. In fact, decreased iron stores or decreased availability of iron

represent the most common cause of resistance to the effect of EPO agents. An ideal test to evaluate iron status in CKD patients would accurately indicate whether the patient has sufficient amount of iron available to support achievement and maintenance of Hb target, and an excessive amount of body iron. Unfortunately, no test exists with accomplishes either of these goals and which is practical to administer. Currently, the two best test of iron status are the serum ferritin and the present transferrin saturation (TSAT). Serum ferritin is the most widely used test for the assessment of storage iron, for which the 'gold standard' remains the examination of a bone marrow aspiration stained for iron[42] .However, serum ferritin values have to be interpreted with caution in CKD patients since it may be affected by inflammation or malnutrition, especially in dialysis patients in whom subclinical inflammation may be present[43] .Serum ferritin values <30 mg/L is indicative of severe iron deficiency and are highly predictive of absent iron stores in bone marrow [44,45]. According to NKF-KDOQI Clinical Practice Guidelines for Anemia in CKD, the recommended serum ferritin target to iron therapy in CKD-5 D patients should be >200 ng/mL, while in CKD-5 no D patients >100 ng/mL. CKD-5 D patients with a ferritin target up to 400-ng/mL showed a final ESA doses 28% lower than those in the lower (200-ng/mL) ferritin group, suggesting that higher ferritin target is well tolerated and reduce reduces the requirements for ESA[46] .There is no current evidence available to support treating most patients with serum ferritin levels greater than 500 ng/mL. A therapeutic response to iron therapy in a patient with a ferritin level greater than 500 ng/mL is unlikely. The percent TSAT (serum iron multiplied by 100 and divided by total iron binding capacity: TIBC) reflects iron

that is readity available for erythropoiesis. The TIBC measures circulating transferring. The transferrin molecule contains two binding sites for transporting iron from storage sites to red progenitor cells. A TSAT of 50% indicate that half of the binding sites are activated by iron.

The distinction between absolute and functional iron deficiency is essential to understanding what constitutes adequate TSAT & circulating ferritin concentrations in ESA-treated CKD patients. In normal subjects, iron deficiency is considered "absolute" when iron store is depleted (circulating ferritin levels <12 ng/mL, and iron delivery is impaired as indicated by TSAT below 16%). Absolute iron deficiency in CKD patients has been defined as a circulating ferritin values <100 ng/mL and TSAT levels lower than 20%. Differently, functional iron deficiency results when there is a need for a greater amount of iron to suppor t hemoglobin synthesis than can be released from iron stores. This clinical situation can be observed in a chronic pharmacological stimulation with ESA in CKD patients with adequate iron stores, and it is characterized by a reduction in TSAT percent despite normal or elevated circulating levels of ferretin[45,46] .A TSAT lower than 20% in CKD-5 D patients has been traditionally considered to be an indicator of iron deficiency. A common clinical problem is distinguishing between functional iron deficiency and inflammatory iron block, since the TSAT could be above the 20% and circulating ferritin could be 100 to 700 ng/mL in both clinical situations. During functional iron deficiency, ESA treatment induces a decrease in circulating ferritin levels, which however remain elevated (generally more than 100 ng/mL). In contrast, inflammatory process is characterized by an abrupt increase of serum ferritin levels, that is associated with a

sudden drop in the TSAT. Measurement of high sensitivity C-reactive protein (CRP) may be indicated if occult inflammation is a concern. In this situation, no further intravenous (IV) iron should be administrated until the inflammatory condition has resolved. Reticulocyte count can be obtained with automated CBC testing, and may be high in patients who have active blood loss or hemolysis, and may be low in hypoproliferative erythropoiesis with anemia. Other tests of iron status, such as percentage of hypochromic red blood cells and reticulocyte Hb content may be used instead of, or in addition to, TSAT and ferritin levels if available. Hepcidin is a recently discovered peptide hormone regarded as the key regulator of iron entry into the plasma [(47)],is up-regulated by inflammation and increased iron stores and down-regulated by iron depletion. Hepcidin blocks iron release from the macrophages, limiting iron availability for erythropoiesis. Elevated serum levels of the bioactive hepcidin isoform, have been consistently reported in CKD5 D patients[(48.49)].however, determination of circulating hepcidin levels has not been shown to be clinically useful or superior to more standard iron status tests in patients with CKD[(50)].Folate and vitamin B12 deficiency are uncommon but important causes of treatable anemia, typically associated with macrocytic red blood cell (RBC) indices. The prevalence of vitamin B12 and folate deficiency in CKD-5 D patients is about 10%, and limited data are available in CKD-5 no D patients. Nonetheless, since these deficiencies are easily correctable, and in the case of vitamin B12 may indicate other underlying disease processes, assessment of folate and vitamin B12 levels are generally considered standard components of anemia evaluation, especially in the presence of macrocytosis.

2.5. Use of iron to treat anemia in CKD:

Iron is an essential mineral for heme synthesis, and adequate amounts of it are required for the production of new erythrocytes. Erythropoietic stimulation during anemia treatment in CKD patients, induces a greater utilization of iron available to satisfy the increased demands of the bone marrow. Under these conditions, the amount of iron usable could become inadequate[51].Therefore, iron supplementation in CKD patients with anemia is used to assure adequate iron stores for erythropoiesis, correct iron deficiency, and, prevent iron deficiency from developing in those patients receiving ESA treatment. Correction of iron deficiency with oral or intravenous iron supplementation can reduce the severity of anemia through the improve of erythropoietic response to ESA treatment. [52,53]

Iron supplementation, particularly with intravenous iron, can increase erythropoiesis and raise Hb levels even when TSAT and ferritin circulating values are not indicative of absolute iron deficiency, and when bone marrow studies reveal adequate iron stores[54,55] . Due to the limited diagnostic utility of serum ferritin and TSAT test to estimate body iron stores, prescription of iron therapy in patients with CKD is complicated, which makes it difficult to predicting a Hb response to iron supplementation[56].The prescription of iron therapy should be based on an assessment that an increase in Hb level is desirable in order to avoid transfusion or reduce the symptoms of anemia related. In addition, the potential adverse effects of iron supplementation should be considered taking into account appropriately outweighed by the expected treatment benefit. Iron supplementation could be in the form of oral or intravenous (IV) while the use of intramuscular iron has largely been abandoned. Each administration route has its own potential advantages and disadvantages. Oral iron is less expensive, readily available, and does not

require IV access, a particular concern in non dependent-HD CKD patients. Despite oral route is generally well tolerated and it is not associated with severe adverse effects, gastrointestinal side effects such as nausea, dyspepsia and diarrhea are common and may limit adherence[57]. In addition, variable gastrointestinal tract absorption associated with gastrointestinal intolerance, can affect the treatment efficacy, penalizing the choice of this route of administration. IV iron avoids concerns about medication adherence and efficacy in treating iron deficiency, but requires IV access and has been associated with infrequent but severe adverse reactions. The most dangerous adverse reaction to IV iron treatment is anaphylaxis, which is the most serious expression of hypersensitivity reactions (HSR) [58]. HSR are quite rare but they could be fatal if not managed promptly[59] . They used to be more common with older formulations of high molecular weight iron dextran (HMW-ID) than with newer preparations [60,61].Similar to iron dextran, new iron molecules with large molecularweight have been developed. Given the reduced amount of free iron released following administration, they may have an improved safety profile. However, post-marketing data are still inadequate to draw definitive conclusions and new molecules may be object of over reporting. The optimum route of iron administration in CKD patients is still controversial. IV iron is more effective than oral iron in HD patients in replenishing iron stores, achieving a sustained Hb response, reducing the need for red blood cell transfusions [62] , and reducing the required dosage of ESA [63,64]. In non-dialysis dependent CKD patients there is no widely accepted consensus on whether IV or oral iron should be used as first-line therapy in CKD-related anemia. Despite the potential benefits of oral iron, that include the low cost and the easy administration, its use is limited by poor gastrointestinal adsorption and high rate of adverse events. [57,65–66]

Oral iron is typically prescribed to provide approximately 200 mg of elemental iron daily. Oral administration should be given between meals (e.g., 2 hours before or 1 hour after a meal). For patients who have difficulty tolerating oral iron supplements, it is possible prescribe smaller, more frequent doses; start with a lower dose and increase slowly to the target dose; try a different form or preparation; or take at bedtime. In same CKD patients, daily smaller doses of oral iron may be useful and better tolerated. Although ferrous sulfate is commonly available and inexpensive, other oral iron preparations may also be used; there is not significant evidence to suggest that other oral iron formulations are more effective or associated with fewer adverse side effects than ferrous sulfate. If the goals of iron supplementation are not met with a 1–3 month course of oral iron, it is appropriate to consider IV iron supplementation. Iron dextran (ID) formulations carry a black box warning about fatal anaphylactic reactions, likely because of antibodies to the ironcarbohydrate or ID complex or the dextran component, particularly with high-molecular-weight ID (HMW-ID). The introduction of low-molecular-weight ID (LMW-ID) substantially reduces the risk of anaphylaxis. With ID therapy, test doses are required, along with an observation period for antibody reactions. Newer IV irons ferric gluconate and iron sucrose, that do not contain dextran, have a better safety profile. Chertow et al [(67)] .compared absolute rates of life-threatening HSR reported by the FDA from 2001 to 2003. For four different parenteral iron preparations (iron sucrose, ferric gluconate, LMW-ID, and HMW-ID), HSR were 0.6, 0.9, 3.3, and 11.3 per million patients, respectively. Ferumoxytol is the newest IV iron formulation to enter in the market [(68)]. It is a superparamagnetic iron oxide nanoparticle coated with a low molecular weight semisynthetic carbohydrate. It helps to isolate the bioactive iron from plasma components until the iron-

carbohydrate complex enters the reticuloendothelial system macrophages of the liver, spleen and bone marrow. The iron is released from the iron-carbohydrate complex within vesicles in the macrophages. Iron then either enters the intracellular storage iron pool (e.g., ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells.

2.6. Use of erythropoietic-stimulating agents to treat anemia in CKD:

The main cause of anemia in CKD is a loss of kidney endogenous erythropoietin (EPO) production capacity, but more recently other conditions able to aggravate this effect have been proposed, such as a derangement in oxygen sensing[69]. The introduction of recombinant human erythropoietin (rHuEPO) into clinical practice in the 1980s was a major innovation in the treatment of the anemia of patients with CKD. The development of rHuEPO was aimed at replacing the insufficient EPO production related to CKD progression. Thus, the rHuEPO therapy was considered as a useful therapy for dialysis dependent CKD patients, whose hemoglobin dropped to extremely low levels, making them transfusion-dependent. The immediate improvement in symptoms of anemia with the administration of rHuEPO in CKD patients was associated with reduced need for blood transfusions, resulting in risk of transmission of bloodborne viral diseases, such as hepatitis B and C, less allosensitization, predispose to long waiting times or failure to receive a kidney transplant, transplant rejection, and reduced risk of hemosiderosis [70] . In many observational studies, the gradually increased and often the normalization of Hb values, showed an inversely proportional association to certain intermediate outcomes such as left ventricular hypertrophy[71] ,as well as patient outcomes hard as cardiovascular events hospitalization [72], and death [73]. At the beginning, the use of rHuEPO has been limited to dialysis patients with the most serious forms of anemia. In the

following years, its use has been extended to the majority of dialysis patients with renal anemia, and, later, also in anemic patients with CKD 4-5 in countries where the high cost of rHuEPO did not limit number of patients who can benefit from this treatment. In this period, Hb targets also increased progressively, often into the range of normal values. The idea of a complete correction of anemia was based on improving outcomes in the medium and long term reported in observational studies [71,72,74]. The US Normal Hematocrit Trial by Besarab et al [75].was the first of a series of randomized controlled trials (RCTs) which cast serious doubt on the assumption that full anemia correction should be achieved in the majority of dialysis patients. Patients who achieve a normal Hb showed a greater number of myocardial infarcts, primary events and deaths than those in which anemia was partially corrected anemia with epoetin. The study was stopped early due to inability to prove the primary hypothesis. The double-blind Canada-Europe trial by Parfrey et al[74] .in CKD 5HD patients without symptomatic heart disease (18% with diabetic nephropathy) failed to demonstrated a beneficial effect on left ventricular volume and mass index in the full anemia correction regime using epoetin-alfa (Hb target=13.5–14.5 g/dL), compared to partial correction one (Hb target=9.5–11.5 g/dL). In the CREATE study by Drueke et al[76]. in CKD stage 3-5 patients, was not demonstrate a superiority of full anemia correction (Hb target=13.0–15.0 g/dL) in terms of cardiovascular events, as compared to partial correction of anemia (Hb target=10.5–11.5 g/ dL), when starting ESA therapy at an earlier stage than end-stage renal disease (ESRD) using epoetin-beta. Dialysis therapy was required in significantly more patients in the high Hb group than in the low Hb group. However the rate of fall of GFR in the two groups during the 3 year study was similar. Also the US CHOIR study by Singh et al[77] .was prematurely stopped after an interim analysis with a median study

duration of 16 months. This study failed to demonstrate a superiority of full anemia correction (Hb targets=13.5 g/dL) by ESA administration in terms of cardiovascular events and death, as compared to partial treatment of anemia (Hb targets=11.3 g/dL), in patients with CKD 3–4 patients using epoetin alfa. Finally, the international trial of darbepoetin-alfa in type 2 diabetes and CKD (TREAT) by Pfeffer et al[78] . that examined cardiovascular and kidney outcomes in CKD 3–4 patients, not significant differences were found neither in cardiovascular event and death nor in ESRD, in patients with full anemia correction (Hb targets=12.5 g/dL) compared partial treatment of anemia (Hb targets=10.6 g/dL), Assessment of ESAs in CKD using meta-analysis is problematic because of the heterogeneity of patients entered, the different quality and research designs of the RCTs performed, and differences in definitions of endpoints. The most recent meta-analysis[79] concluded that higher Hb concentrations in CKD increases risk for stroke, hypertension, and vascular access thrombosis, and may perhaps increase risk for death, serious cardiovascular events or ESRD. According to the interpretations of the combined results of the recent major RCTs, the target Hb values exceeding 11.5 g/dL in adult CKD patients can cause more harm than benefit. The update of the 2006 KDOQI anemia guideline in 2007, had already led to the recommendation to limit the upper the target Hb to 12 g/dL, and do not exceed 13 g/dL[80]. Regarding the initiation of therapy ESA, dose adjustments ESA and rates of change, the objective is a rate of increase in Hb concentrations of 1.0 to 2.0 g/dL per month[35]. The Hb rate of increase varies greatly as a function of individual ESA responsiveness. Poor responders are more likely female, patients with history of cardiovascular disease, iron deficiency and inflammation, and overweight[81]. The response also depends on initial dose, dosing frequency, and route of administration. However, the last two concern

epoetin-alfa, epoetinbeta, and darbepoetin but not CERA (continuous erythropoietin receptor activator) [methoxy polyethylene glycol-epoetin-beta]). Table 3 compares the different erythropoietin-stimulating agents. Epoetin-alfa or epoetin-beta dosing usually starts at 20 to 50 IU/ kg body weight three times a week. Darbepoetin-alfa dosing usually starts at 0.45 mg/kg body weight once weekly by subcutaneous (SC) or IV administration, or 0.75 mg/kg body weight once every 2 weeks by SC administration. CERA dosing starts at 0.6 mg/kg body weight once every 2 weeks by SC or IV administration for CKD ND and CKD5D patients, respectively, or 1.2 mg/kg body weight once every 4weeks by SC administration for CKD ND patients. Higher baseline Hb concentrations

require lower initial ESA doses, except for CERA for which there is no initial dose change. However, ESA requirements should be evaluated or reevaluated each time a patients with CKD is hospitalized. ESA responsiveness may be modified profoundly during Disease states such as severe infections or postsurgery. In recent years, the scenario of ESA has become complex due to the appearance of biosimilars epoetin in trying to contain production costs. The European Union is currently the most advanced region in terms of having a developed regulatory pathway for biosimilar products. Medicines legislation creating the regulatory pathway for biosimilars was introduced in Europe in 2004. The European Medicines Agency (EMA)/Committee for Human Medicinal Products (CHMP) issued an overarching biosimilars guideline[82]. To obtain marketing authorization for a biosimilar, comparative quality studies with an approved reference epoetin, and non-clinical and clinical safety and efficacy studies are required. Two biosimilar epoetins (substances HX575 and SB309) proved sufficient analogy to the innovator epoetin alfa (Eprex®/Erypo®) in preclinical and clinical studies according to the EU

guidelines. HX575 has been approved under three different trade names: Binocrit® (Sandoz), Epoetin alfa Hexal® (Hexal Biotech) and Abseamed® (Medice Arzneimittel Putter). These co-marketed products are true 'bioidenticals' which may be substituted among themselves. Epoietin zeta or SB309 has been approved under two different trade names: Silapo® (Stada) and Retacrit® (Hospira), which are bioidenticals among themselves. The Australian Therapeutic Goods Administration (TGA) has approved the 'epoetin lambda' (Novicrit®, Novartis Pharm, Australia) with sufficient analogy to the epoetin alfa. An 'epoetin kappa' has been available in Japan since 2010, which was approved as a biosimilar to epoetin alfa. However, the isoelectric and isoform profile of epoetin kappa differs greatly from the profile of other epoetins. In 2009, S. Korea released a draft guidance on biosimilars and in the same year Singapore's drug regulation agency, the Health Sciences Authority (HSA), issued guidelines on the regulatory registration of biosimilars, which was mainly adapted from EMA biosimilar guidelines.[35]

2.7.Iron over load due to blood transfusion:

Iron overload is a major concern in patients with congenital and acquired anemias for whom regular transfusions are needed. Under normal conditions, iron absorption and loss are balanced at~ 1mg/day. Transfused blood contains (200-250) mg of iron per unit. The body has no mechanism for excreting this excess iron. Moreover, patients with TM and other anemias characterized by ineffective erythropoiesis absorb excess iron despite iron overload because of production of GDF15 and possibly other proteins (eg, TWSGI) from erythroblasts, which inhibit hepcidin synthesis.1 Untreated transfusional iron load results in damage to the liver, endocrine organs, and most importantly to the heart.[83]

2.8.Iron profile:

Iron stores in normal subjects very between approximately 800 mg to 1200 mg, depending on body size[84]. Although phlebotomy studies suggest that normal iron stores may be as high as 1200 to 1500 mg.[85]

2.8.1.Serum Iron:

Iron is carried in the plasma bound to the protein transferrin . This molecule binds two atoms of iron as Fe3+ and delivers iron to cells by interaction with membrane transferrin receptors.[86]

2.8.2.Serum ferritin:

Ferritin is protein found inside cells that stores iron so the body can use it later. A ferritin test indirectly measures the amount of iron in the body. The amount of ferritin in the body is directly related to the amount of iron stored in the body.[85]

Ferritin is the main storage protein for iron and absolute iron deficiency , according to the kidney disease out comes quality initiative (K/DOQI), correlates with serum ferritin less than 100ng/mL. [87]

2.8.3.Total iron binding capacity (TIBC):

It's usually measured by adding un-excess of iron and measuring the iron retained in solutions after the addition of a suitable reagent such as light magnesium carbonate or an-iron exchange resin that remove excess iron.[88]

2.8.4.Tranferrin saturation (TSAT):

Transferrin is a specific protein that transport iron from the site of absorption to developing erythroblast and to store site.

The TSAT corresponding to circulating iron, is the serum iron divided by the TIBC.[87]

2.9. Previous study:

-First study in 1994 done by Joseph W. EschbacH et al., who studied 166 hemodialysis patients and reported that the iron status was increase[89].

-Second study done by Canavese C, Bergamo D, Ciccone G, et al. in 2004 who was evaluatethe iron profile in 40 transfused hemodialysis patient and reported that 30% of the patients were normal and 70% iron were over load [90] .

-Third study by Ramakrishna Devaki1, Pragna Raoet al. in 2013 who studied 290 hemodialysis patients and reported that 31% of the dialyzed patients were over load and lowered transferrin level in compared with control group [91] .

Fourth study done by Ashwag Abdalla Osman Mahgoub and Ibrahim Khider Ibrahim. in 2017 who studied 40 iron profile in hemodialysis patients and reported that serum iron and serum ferritin of the patients under dialysis were significantly higher , While TIBC was significantly lower as compared to healthy control individual , a significant correlation between the age of patients and TIBC , no statistical significant between age and serum iron and serum ferritin, and their was no statistical significant correlation between iron profile and patients gender and duration of dialysis[92] .

3.Materials and Methods

3.1.Study design:

This is a descriptive cross-sectional case-control study to evaluate iron profile in chronic renal failure patients in Shendi locality in the River Nile State Sudan during the period of (March 2018—July 2018).

3.2. Study area:

The study was conducted at Almek Nimir University Hospital which located in Shendi town in Sudan. Shendi is a town in Northern Sudan, situated on the east bank of the Nile (150 km) Northeast of Khartoum. Shendi is also about (45 km) southwest of the ancient city of Meroe. Located in the River Nile state, Shendi is the center of the Ja'aliin tribe and an important historic trading center. Its principal suburb on the west bank is Al-Matamma. A major traditional trade route across the Bayuda desert connects Al-Matamma to Marawi and Napata, (250 km) to the Northwest.

3.3. Study population:

A total of (30) samples collected of Study group of chronic renal failure patients and (10) samples collected of healthy individuals as control group.

3.4. Inclusion criteria:

Patients of both sexes with chronic renal failure undergoing hemodialysis (who depend on blood transfusion or not and receiving iron and erythropoietin therapy or not).

3.5. Exclusion criteria:

Patients with other severe diseases such as heart disease, liver disease, hematological diseases .

3.6. Data collection tools:

Data was collected using self-administrated pre-coded questionnaire which specifically designed to obtain information that helped in study.

3.7. Blood Sampling:

3 mL venous blood collected using sterile disposable plastic syringe after cleaning the venipuncture area with (70%) ethanol, the blood collected in plain container and separated by centrifugation to obtain serum.

3.8.Materials:

- Plain containers.

-Syringes.

-Centirfuge.

-Spectrophotometer.

-Automatic pipettes. (10-100ul, 100-1000ul).

3.9. Methods:

Iron profile was done by using spectrophotometer.

3.9.1.Serum iron (iron ferrozine):

3.9.1.1.Principle of the method:

Transferrin-bound ferric ions in the sample are released by guanidinum and reduced to ferrous by means of ascorbic acid . ferrous ions with ferrozine forming acoloured complex that can be measured by spectrophotometry.

3.9.1.2.Reagent:

-Reagent A: 4x40 mL. guandinium chloride 1.0 molL, acetate buffer 0.4 mol/L,pH 4.0.

-Reagent B: 4x10mL. Ferrozine 8 mmol/L, ascorbic acid 200 mmol/L.-

-Iron standard. 1x5 ml. iron 200 ug/dL (35.8 umol/L). aqueous primary standard.

3.9.1.3. Procedure:

1- The reagent brought to the room temperature.

2.Into labeled test tube the following pipette:

-200 uL of distilled water into reagent blank tube.

-200 uL of sample into tube of sample and sample blank tube.

-200 uL of iron standard(S) into tube of standard tube.

-1mL of reagent (A) into sample bank tube.

-1mL of working reagent into reagent blank ,sample blank and standard tubes.

3-Mixed thoroughly and the tubes stood for 5 mins at room temperature.

4- Absorbance (A) of the sample blank read at 560 nm against distilled water.

5- Absorbance (A) of the sample and of the standard read at 560 nm against reagent blank.

3.9.1.4: calculations:

The iron concentration in the sample is calculated using the following formula:

$A_{sample} - A_{sample\ blank} / A_{standard} \times C_{standard} = C_{sample}$

Normal range :

Men :65-175 ug/dL

Women: 50-170 ug/dl

3.9.2.Total iron binding capacity (Fe^{3+} / magnesium hydroxide carbonate) :

3.9.2.1.Principle of the method:

Excess of Fe^{3+} is added to saturate serum transferrin . un complexed Fe^{3+} is precipitated with magnesium hydroxide carbonate and iron bonded to protein in the supernatant is then spectrophotometrically measured.

3.9.2.2. Reagent :

Reagent A:1x50 mL. iron chloride (III) 0.12 mmol/L.

-Reagent B: 3.10 g magnesium hydroxide carbonate (powder).to be dispensed using the enclosed plastic spoon.

3.9.2.3: procedure:

1-The following pipette into labeled test tubes:

-0.5mL of sample .

-1.0 mL of reagent (A).

2- Mixed thoroughly and stood for 5-30 minutes at room temperature.

3- To each tube one spoonful of reagent (B) was added.

4-Mixed thoroughly and the tubes standed for 30-60 minutes at room temperature .during this time mixed thoroughly several times.

5- Centrifuged at 300 r.p.m for minutes.

6- The supernatant collected carefully.

7- The iron concentration in the supernatant measured, using the kit iron – ferrozine .

3.9.2.4 . calculations:

Total iron binding capacity(TIB)= iron concentration in the supernatant x3.

Normal range:

Infant: 100-400ug/dl

Adult: 250-425ug/dL

3.9.3.Ferrtin (latex) :

3.9.3.1.principle of the method:

Serum ferritin causes agglutination of latex particles coated with anti-human ferritin antibodies. The agglutination of the latex particles is proportional to the ferritin concentration and can be measured by turbidimetry.

3.9.3.2.Reagent:

-Reagent A: glycine buffer 170 mmol/L, sodium chloride 100 mmol/L sodium azide g/L pH .

-Reagent B: suspension of latex particles coated with anti-human ferritin antibodies, sodium azide 0.95 g/L.

3.9.3.3. procedure:

1-The working reagent and instrument brought to 37C^{o}.

2-The instrument adjusted to zero with distilled water.

3-Into cuvette the followings pipette:

-1mL of working reagent.

-30 uL of sample or standard.

4- Mixed and the cuvette inserted into the instrument. The stop watch started.

5- The absorbance read at 450 nm after 10 seconds (A_1) and after 5 minutes.

Normal range:

Children:7-140ug/dL

Men: 20-250ug/dL

Women:20-200ug/dL

3.9.4. Ethical consideration:

The consent of the selected individuals to the study was taken after being informed with all detailed objectives of the study and it is health emphasis in the future.

3.9.5. Data analysis:

The collected data code in master sheet and proceed for analysis using SPSS version 11.5 . (mean, standard deviation, P.value by using independent T.test).

4.Result

Demographic and clinical data:

A total of (30) blood samples collected from chronic renal failure patients and (10) samples collected as control from healthy individuals include frequency of sex was 22 males (73.3%) and 8 females (26.7%)as shown in Table (4.1). frequency of age groups (31-50) years old was 20 (66.7%) ,(51-70) years was 7.0 (23.3%) and (71-100)was 3.0 (10.0%) in the study group . Table (4.2) .

Table (4.1.): Distribution of study population according to sex:

Sex	Frequency	Percent%
Male	22	73.3%
Female	8	26.7%
Total	30	100.0%

Table (4.2): Distribution of study population according to age:

Age	Frequency	Percent%
(31-50)yrs	20	66.7%
(51-70)yrs	7	23.3%
(71-100)yrs	3	10.0%
Total	30	100.0%

According to duration of disease frequency from (1-4) years was 21 (70%) ,from(5-8) years was 6.0 (20.0%) and from (9-12) years was 3.0 (10.0%).Table (4. 3).

Table (4. 3): Distribution of study population according to the duration of diseases:

Duration (years)	Frequency	Percent%
(1-4)yrs	21	70%
(5-8)yrs	6	20.0%
(9-12)yrs	3	10.0%
Total	30	100.0%

Regarding to dependency on blood transfusion 7 of the patients (23.3%) were transfusion dependent and 23 of them (76.7%) were non-transfusion dependent. Table (4.4).

Table (4.4): Distribution of study population according to dependency on blood transfusion:

Dependency on blood transfusion	Frequency	Percent%
Yes	7	23.3%
No	23	76.7%
Total	30	100.0%

According to use of iron therapy 25 of the patients (83.3%) were used iron therapy and 5 of them (16.17%) were not use iron therapy .Table (4.5).

Table (4.5): Distribution of study population according to use iron therapy:

Iron therapy	Frequency	Percent%
Yes	25	83.3%
No	5	16.6%
Total	30	100.0%

According to presence of another chronic disease 14 of the patients (46.7%) were have no another chronic disease , 5 of them (16.7%) have diabetes mellitus and 11 (36.7) have a hypertension . Table (4. 6).

Table (4. 6): Distribution of study population according to presence of another chronic disease

Presence of chronic disease	Frequency	Percent%
No	14	46.7%
DM	5	16.7%
Hypertension	11	36.7%
Total	30	100.0%

According to study population 30 participants (70%) were case and 10 (25%) were control. Table (4. 7).

Table (4. 7): Distribution of study participants

Group	Frequency	Percent%
Case	30	75%
Control	10	25%
Total	40	100%

Laboratoy Data:

The results of the present study showed that the mean of the serum iron ,serum ferritin and TIBC in case group were(182.2667ug/dL), (267.4000ug/L) and (195.2333ug/dL) respectively and in control group the mean values of the serum iron ,serum ferritin and TIBC were (133.1000ug/dL) , (183.2000ug/L) and (291.4000ug/dL) respectively . Table (4.8).

Table (4.8) : Comparison between Case and control in iron profile

Parameter	Group	Number	Mean	Std. Deviation	P.Value
S.iron	Case	30	128.2667	61.45306	0.020
	Control	10	133.1000	30.03868	
Ferritin	Case	30	267.4000	104.52936	0.022
	Control	10	183.2000	65.30578	
TIBC	Case	30	195.2333	85.32643	0.005
	Control	10	291.4000	94.24578	

The mean of the of the serum iron ,serum ferritin and TIBC in male were (172.8182ug/dL), (258.5909ug/L) and (196.3182ug/dL) respectively and in female the mean of the of the serum iron ,serum ferritin and TIBC were (208.2500ug/dL) ,(291.6250ug/L) and (192.2500ug/dL) respectively . Table (4.9).

Table : (4.9) Correlation between iron profile and gender of patient

Parameter	Gender	Number	Mean	Std. Deviation	P.Value
S.iron	Male	22	172.8182	58.87164	0.166
	Female	8	208.2500	64.77378	
Ferritin	Male	22	258.5909	93.14743	0.454
	Male	8	291.6250	135.36083	
TIBC	Male	22	196.3182	97.68091	0.910
	Female	8	192.2500	39.03753	

The mean of the of the serum iron ,serum ferritin and TIBC for the age group (31-50) years old were (184.3000ug/dL),(273.4000ug/L) and (200.2000ug/dL) respectively , for the age group (51-70) years old the mean values of the serum iron ,serum ferritin and TIBC were (180.2857ug/dL) , (250.1429ug/L) and (158.7143ug/dL) respectively and for the age group (71-100) years old were (173.333ug/dL), (267.6667ug/L) and (247.3333ug/dL) respectively . Table (4.10)

Table(4.10):Comparison between iron profile and age of the patients:

Parameter	Age(years)	Number	Mean	Std. Deviation	P.Value
S.iron	(31-50)yrs	20	184.3000	68.02871	0.958
	(51-70)yrs	7	180.2857	50.96638	
	(71-100)yr	3	173.3333	53.16327	
	Total	30	182.2667	61.45306	
Ferritin	(31-50)yrs	20	273.4000	103.88729	0.887
	(51-70)yrs	7	250.1429	126.13013	
	(71-100)yr	3	267.6667	82.30634	
	Total	30	267.4000	104.52936	
TIBC	(31-50)yrs	20	200.2000	80.15748	0.301
	(51-70)yrs	7	158.7143	55.05365	
	(71-100)yr	3	247.3333	162.63558	
	Total	30	195.2333	85.32643	

According to duration of disease the mean of the of the serum iron ,serum ferritin and total TIBC for a disease duration of (1-4) years were (177.4286 ug/dL),(266.7143ug/L) and (189.7619ug/dL) respectively , for duration of (5-8) years the mean values of the serum iron ,serum ferritin and TIBC were (206.1667ug/dL) , (284.0000 ug/L) and (197.5000ug/dL) respectively and for duration of (9-12) years the mean values of serum

iron ,serum ferritin and total TIBC were (168.3333ug/dL), (239.0000ug/L) , and (229.0000ug/dL) respectively. Table (4.11).

Table(4.11) : Comparison between iron profile and duration of the disease

Parameter	Duration of disease (years)	Number	Mean	Std. Deviation	P.Value
S.iron	(1-4)yrs	21	177.4286	59.61004	0.567
	(5-8)yrs	6	206.1667	61.35932	
	(9-12)yrs	3	168.333	86.96168	
	Total	30	182.2667	61.45306	
Ferritin	(1-4)yrs	21	266.7143	85.90643	0.839
	(5-8)yrs	6	284.0000	153.03986	
	(9-12)yrs	3	239.0000	155.04515	
	Total	30	267.4000	104.52936	
TIBC	(1-4)yrs	21	189.7619	67.26067	0.768
	(5-8)yrs	6	197.5000	118.86253	
	(9-12)yrs	3	229.0000	100.25468	
	Total	30	195.2333	85.32643	

5. Discussion ,Conclusion and Recommendations

5.1.Discusion:

Chronic kidney disease (CKD) is an irreversible progressive reduction in renal function an important source of long term morbidity and mortality. It has been estimated that CKD effect more than 20 million people in the united estate [93]. Anemia commonly occurs in people with CKD, when kidneys are damaged, they do not make enough EPO as a result the bone marrow makes fewer red cells, causing anemia. Other causes of anemia in CKD in include blood loss from steps of hemodialysis, to prevent of anemia to need frequent red blood cell transfusion and EPO therapy, due to blood transfused and EPO therapy to lead of iron over load . [91]

The result of this study denoted that the patients with chronic renal failure have increase level of serum iron and serum ferrtin and lowered level of TIBC .

The present study revealed that increase serum iron and serum ferritin level (p value 0.020 , p value 0.022) respectively. And lowered TIBC and (p value 0.005) , were statistically significant different in patients with chronic renal failure compared with control group . results of this current study agreed with study done by Joseph W. EschbacH et al. who revealed high serum iron in hemodialysis patients . and another study done by Canavese C, Bergamo D, Ciccone G, et al. who reported that 30% of the patients were normal and 70% iron were over load.

Also the results of this study confirmed that there are no stastistical correlation between the age of patients and serum iron (P.value 0.958), serum ferritin (P.value 0.887) and TIBC ((P.value 0.301) . and this results disagreed with study done by Ashwag Abdalla Osman Mahgoub and Ibrahim Khider Ibrahim in Al-Neelain University, Khartoum, Sudan which showed a significant correlation between the age of patients and

TIBC , and agreed with the same study in that no statistical significant between age of the patients and serum iron and serum ferritin.

According to the patients gender there is no statistical significant correlation between iron profile and patients gender (p.value 0.166), (p.value 0.454) and (p.value 0.910) for serum iron, serum ferritin and TIBC rspectivley .

Regarding to the duration of disease this study confirmed that there was no statistical significant correlation between iron profile and duration of disease (p.value 0.567), (p.value 0.839) and (p.value 0. 768) for serum iron, serum ferritin and TIBC respectively , and this agreed with the study done by Ashwag Abdalla Osman Mahgoub and Ibrahim Khider Ibrahim which showed , that no statistical significance between age of the patients and serum iron and serum ferritin and there was no statistical significance between gender of the patients and duration of disease and iron profile.

5.2. Conclusion:

- Serum iron and serum ferritin were higher in chronic renal failure patients when compared to healthly indiviuals in the control group.
- Total iron binding capacity was lower in chronic renal failure patients when compared to healthly indiviuals in the control group.
- Age, gender of the patients and duration of disease have no affect on iron profile in chronic renal failure .

5.3. Recommendations:

-Iron profile should be checked regularly in patients with chronic renal failure.

-Health education about renal failure should improve.

-Further studies in this topic with increasing sample size and study area to give accurate results.

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Appendix I

University of Shendi

Faculty of Graduate Studies and Scientific Research

Assessment of Iron Profile among Sudanese Patients with Chronic Renal Failure in Shendi Town

Questionnaire

-Personal data:

1-Identification number ☐

2-Name……

3-Age…..…..……

4-Gender…….....**.....**

5-Adress…….……..

-Clinical data:

6-Duration of the disease……..

7-Dependancy on haemodialysis:

-Yes ☐

-No ☐

8- Dependency on blood transfusion:

-Yes ☐

-No ☐

9-Frequency of blood transfusion.. ……..

10-Type of blood product/s transfuses always:

-Whole Blood ☐

-Packed red blood cells ☐

11- Erythropoietin therapy:

-Yes ☐

-No ☐

12-Iron therapy:

-yes ☐

-No ☐

13-Any another chronic disease/s……...

-Iron profile results:

-Serum iron……

-Serum ferittin……..

-Total iron binding capacity……

Appendix II

إقـــرار بالموافقـــة

الاسم :----------

العمر :---------- العنوان :----------

أوافق بمحض ارادتى بالمشاركة في البحث العلمى المتعلق بدراسة قياس مستوى معاملات الحديد في الدم لدي مرضي الفشل الكلوي المزمن في مستشفى المك نمر الجامعى وحدة غسيل الكلي .

الهام منصور الطيب محمد

بعد أن شرحت لي بأنه لا يترتب عليه أي أذى جسدي أو نفسي واعلم أن المشاركة في هذا البحث لن تؤثر بأي حال من الأحوال في الرعاية الطبية التي أتلقاها كما أنه يحق لي بدون ابداء أسباب الإنسحاب من هذا البحث في أي مرحلة من مراحله.

البحث بإشراف :

د.حمزة أحمد حسن

التوقيع : ---------- التاريخ :----------