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Erythropoietin Hormone in Patients with Kidney Failure

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Abstract: Background: Studies on patients with different stages of chronic kidney diseases (CKD) have looked into the relationship between renal outcomes and iron status markers such as serum ferritin and transferrin saturation (TSAT). The relationships, meanwhile, were erratic and hotly contested. Thus, our goal was to find out if serum ferritin levels and TSAT were related to kidney outcomes in such particular populations. In this study, 109 patients were prospectively tracked after being admitted for CKD education and evaluation.

Aim of the study:. Estimation of serum Erythropoietin (EPO) and Ferritin levels in those who were suffering from persistent renal failure with the third uterus compared to healthy people.

Materials and methods: The study included a total of 109 samples, and 27 healthy individuals were chosen as a control group. The age range of the participants was between (40-60) years, including both genders. Specimens were obtained from outpatient clinics between January 2024 and May 2024.

Results: The present study showed a decrease in Erthropotin hormone level in stage 5 kidney disease with dialysis (565.02 ±53.06c) as compared to the controls at p-value <0.05. Furthermore, this study showed an increase packed cell volume (PCV) value in stage 5 with dialysis (27.28 ± 0.91d) as compared with the control group (0.66 ± 0.89 a) at P-value P≤0.05. In addition, a decrease in hemoglobin (Hb) levels was detected in patients with the dialysis stage 5

(8.52 ±0.32[d]).

Keywords: EPO, PCV, CKD

Introduction

Chronic renal failure (CRF) is a global health problem, and this disease is widespread. It casts a shadow over specialists and researchers in understanding and preventing it from spreading among societies through the mechanisms of its work and development and preventing it from reaching its final wombs, which require global agriculture (1). A decline in quantitative functions is often accompanied by anemia, which remains one of the most common phenomena. The visible and characteristic features of the quantum temporal failure remained for more than 150 years. It is a poor form of pellets, showing normocytic and normochromic with normal bone marrow cell production (2). However, anemia in patients with (CRF) is multifactorial, despite the lack of adequate production Erythropoietin hormone (EPO), which is the most important factor in CRF anemia. However, other factors are present, which has roles in contributing to the occurrence of mild anemia, although the use of substitutes for human erythropoietin and other factors stimulates the production of red blood cells, such as erythropoiesis-stimulating agents (ESA), and one of these factors is the shortened life of the blood cell, red blood loss, iron deficiency, deficiency of other nutritional factors, blood tolerance and the presence of uremic inhibitors of erythropoiesis (2,3). Adequate iron storage is essential for maximum benefit from treatment with ESA iron. The remainder is mainly located in the liver and marrow, while ¼ of the body is present in the erythrocytes in the organs. However, due to the frequent demand for iron in the red marrow, the excess iron deficiency is one of the therapeutic agents that stimulates the production of red blood cells, so iron food additives are necessary and commonly used in the period before treatment with EPO, except for the development of the disease and its relationship to anemia, resulting from iron excess due to repeated blood transfusions to patients (4). Hemosiderin and ferritin are the two main molecules in the body that store iron. It is a 13 nm-diameter sphere with a central cavity which is linked with the surface of a molecule through six channels. About 4500 Fe(III) atoms are contained in a cavity, which is made up of 24 heavy (H) and light (L) polypeptide chains folded in four helix bundles. The molecule's molecular weight is about 800,000 kDa when it is completely loaded with iron (7). Ferritin is not present in the majority of somatic cells under typical body iron loading conditions. On the other hand, cells that perform certain iron-related tasks, including storage, might have high ferritin levels. The cytoplasm of these cells contains a significant amount of dormant ferritin messenger RNA (mRNA). Ferritin polypeptide subunits are quickly generated and mRNA is processed when iron enters the cell (8). The process is controlled by the interaction of a cytoplasmic iron regulatory protein with the mRNAs noncoding regions, called iron responsive element (6,9).

When erythropoietin (EPO) was first used in clinical settings over 20 years ago, the way patients with chronic kidney disease (CKD) were managed underwent a radical change. Erythropoietin-stimulating drugs, or ESAs, are analogues of EPO and have been widely used to treat anemia. This has reduced related morbidity and improved functioning, exercise tolerance, cognitive performance as well as general life quality. Additionally, there was a notable decline in cardiovascular (CV) morbidity and mortality. However, since the publishing of the wide scale randomized studies suggesting a higher risk associated to administering large EPO doses targeting to greater levels of hemoglobin, there has been much disagreement regarding the potential hazards of ESA therapy. Furthermore, a careful examination of the mechanisms behind EPO's actions has shown a number of physiologic consequences that go beyond its erythropoietic function and may contribute favorably or unfavorably to these results. Anemia is defined by the WHO as a hemoglobin level less than 120 g/L in women who are not yet menopausal and less than 130 g/L in men (13).

Classical clinical signs provide the basis for the diagnosis of many renal disorders. A doctor,

who is typically a nephrologist, starts by obtaining a complete clinical history and do physical examinations. A doctor would inquire about the patient's medication history, family history, recent infections, exposure to chemicals or toxins, and any other past events that might point to the cause of the patient's kidney illness in addition to the medical background and present symptoms of the patient. Certain disorders are frequently indicated only by the clinical history and time course (30). When a child who was previously healthy has an upper respiratory tract infection, edema in the face and lower limbs, and a urinalysis reveals proteinuria, it is highly recommended that minimal change illness be diagnosed. Similarly, diabetic nephropathy is most probably to be found in patients with history of diabetes who arrives with decreased urine production. Such instances frequently don't need a thorough investigation (such as a kidney biopsy). By using the medical history, physical examinations and supporting test results of patients, a tentative diagnosis can be established.

The study aimed to:

1. Estimation of serum EPO levels in those suffering from persistent renal failure with the third uterus and the four and five (without hemodialysis and under hemodialysis) and compare them to healthy people.
2. Estimating iron deficiency levels (Ferritin) and circulating iron in CKD patients through the stages referred above and compare them to healthy people.

Materials and methods

Study groups: The study adopted a simple non-random selection method based on several variables, including age and gender. 109 samples of kidney failure patients were collected from the dialysis unit at Baqubah Teaching Hospital. Their ages ranged between 40 and 60 years, and specimens were also obtained from outpatient clinics distributed as follows:

1. Control Group :Samples of 28 healthy people who did not suffer from symptoms and signs of kidney failure, diabetes, or thyroid dysfunction were collected, (13 males, 15 females) from the city of Baqubah, their ages ranged between 45-65 years.
2. The second group (group 2): They were patients whose glomerular filtration rate ranging between 30 - 59 ml / min / 1.73 m2, and included 27 patients (18 males, 9 females).
3. The third group (Group 3): They were patients whose glomerular filtration rate was ranging between 15-29 ml /min /1.73 m2, and included 27 patients (11 males, 16 females).
4. Group Four (Group 4): They were patients whose glomerular filtration rate was less than 15 ml/min/1.73 m2, and included 27 patients (11 males, 16 females), before hemodialysis.
5. The fifth group (Group 5): Patients undergoing hemodialysis, which included 28 patients (16 males, 12 females).

In the current study, 10 ml of venous blood was drawn from patients with chronic renal failure who passed away (three, four, fifth without hemodialysis and the fifth under hemodialysis (and for the group of healthy people from Baquba Teaching Hospital / Industrial Quantity Unit for the period from the first of August 2018 to the first of December 2018. (2.5) ml of the blood was placed in tubes containing anticoagulant (EDTA tubes) to estimate the concentration of hemoglobin and the size of the packed cells. The remaining part was placed in dry, clean plain tubes and left at room temperature for a period ranging between 10 - 22 minutes to obtain the serum by separation in a centrifuge (3000 rpm) for 10 minutes. Erythropoietin kit from China/Elabscience was used, and ferritin kit from Calbiotech /USA by Sandwich-ELISA

Statistical analysis:

A specially created questionnaire was used to collect data, which was then entered into a computer system for analysis. The (SPSS-24) version was used to analyze data and results were compared based on various variables at a statistical level of significance ($p \leq 0.01$).

Result and discussion

Table (1) showed that there was a significant decrease at ($p<0.05$) between Stages of kidney failure: the third, fourth and fifth stage without hemodialysis and the fifth stage under hemodialysis in EPO levels compared to healthy people, reaching to 751.94 ± 32.66, 739.72 ± 44.15, 780.36 ± 36.65, 565.02 ± 53.06, 1005.63 ± 39.88 mIU/ml, respectively. These results were consistent with the findings of Schaalan and Mohamed (2016) in their study on 40 patients with AKF, as it was noted that there was a notable decline at ($p<0.05$) in the level of erythropoietin in patients with kidney failure compared to healthy people. Ali and others, (2017) in a study included 50 people with kidney failure, they indicated that there was a significant decrease at $p<0.01$ in EPO levels in patients with CKD in comparison with the controls. Scanlon and Sanders (2007) found that low levels of erythropoietin in the serum of patients with kidney failure may be due to damage to kidney tissue and replacement of the urinary tubules with fibrous tissu , and fibrosis of the capillaries surrounding the renal tubules to form an automatic barrier between the blood and the endothelial cells.

Internal secretion of this hormone in the capillaries as a result of sensitivity to lack of oxygen to produce and release erythropoietin into the blood. Or the reason is due to a lack of renal secretion of erythropoietin.

The decrease in EPO in CKD patients may be a functional response to decreased GFR (Saul, 2006). The decrease may be a result of damage to functional renal tissue in CKD, which impairs the kidney's ability to blind response to O2 processing for EPO production (Haider et al., 2009). The damage to the renal mass and the destruction of the fibroblast cells responsible for EPO production come primarily due to low levels of this hormone (Levy and Akhrov, 2004). This is consistent with the study conducted by (Fehr *et al.*, 2004) who showed decreased erythropoietin production in the CKD group.

EPO lack is the leading cause of anemia due to chronic kidney disease (CKD). Upon treatment with EPO stimulators, few dialysis patients presented with manifest resistance to ESA, which may increase the mortality hazards due to kidney infections (15). ESAs are commonly utilized to treat anemia related to CKD.

Table (4-2): Hemoglobin, PCV, and EPO hormone levels in patients with renal failure compared to healthy people

parameter		**Renal failure**			
	control	Stage 3	Stage 4	Sage 5 Without dialysis	Stage 5 with dialysis
	Group (1)	Group (2)	Group (3)	Group (4)	Group (5)
Numbers	27	27	27	27	28
Gender	13/14	18/9	11/16	11/16	16/12
average age	51.74	52.85	52.62	51.85	51.85
EPO ml\ mIU	1005.63 ± 39.88 a	751.94 ± 32.66^{b}	739.72 ± 44.15^{b}	680.36 ± 36.65 ^{b}	565.02 ± 53.06^{c}
PCV %	40.66 ± 0.89^{a}	36.88 ± 0.12 b	33.55 ± 0.96 c	9.66 ± 0.68 ^{d}	27.28 ± 0.91^{d}
Hb	12.88 ± 0.29 a	11.62 ± 0.43 b	10.51 ± 0.32 c	9.29 ± 0.23^{d}	8.52 ± 0.32^{d}

The reason for the decrease may be that hemodialysis may lead to a group of blood disorders such as anemia. Anemia in renal failure patients may be due to a deficiency in renal production as EPO is produced by the paraglomerular apparatus in the kidney.

Table (1) displays the findings of the current investigation. The level of the hormone erythropoietin in the serum of patients with chronic kidney disease were significantly lower than the control group. In individuals with CKF, the deterioration in kidney function is the primary cause of the drop in erythropoietin levels. Our study's results showed that this hormone's concentration falls with a deterioration in renal function as measured by filtration efficiency and hormone secretion. It is also inversely correlated with the stages of advanced kidney failure. The cells in the kidney's cortex layer that make the hormone erythropoietin are among those whose function deteriorates [11], and that patients suffering from chronic kidney failure experience severe anemia because of a decline in erythropoietin production, which in turn causes a decrease in the marrow's erythrocyte production, which lowers the quantity of RBCs. Most CKD patients also have hypertension and diabetes, which puts additional strain on the cells of kidney—specifically, kidney nephrons and glomeruli—as well as the tubules which perform the function of filtration. The kidneys have a detrimental effect on effectiveness, which lowers the amount of erythropoietin the kidney secretes [12]. By estimating creatinine clearance, the glomerular filtration rate can be determined [13]. Research has indicated that erythropoietin concentrations and the glomeruli's filtration rate are related. Erythropoietin secretion rates also decrease when the glomeruli's filtration level falls below 60 ml min^{-1} [14].

Based on several studies and findings, anemia is one of these disorders that mostly results from errors and disruptions in three natural functions of the human body. Either decreased erythropoietin synthesis happens naturally, or erythrocyte survival rates are lowered.

An additional complication is that patients have lower levels of natural nutrients, such as vitamin B12 or folate. For an extended period, frequent blood transfusions were the main treatment for anemia in individuals with chronic renal disorders.

Nevertheless, there were a number of disadvantages and negative effects of blood transfusion for the patients, chief among them being a reliance on outside sources for necessary blood.

In addition, the patients' fast and frequent blood transfusions resulted in an excess of iron in their bodies. Furthermore, iron free radicals were thought to be toxic and harmful to patients' health, with extremely harmful consequences. The researchers also developed recombinant human erythropoietin (rHuEpo), an alternative medication, to help patients with CKD become less dependent on blood transfusions.

Table (4-3) Iron and ferritin concentrations in patients with renal failure compared to healthy people

Parameter		**Renal failure**			
	control	Stage 3	Stage 4	Sage 5 Without dialysis	Stage 5 with dialysis
	Group (1)	Group (2)	Group (3)	Group (4)	Group (5)
Numbers	27	27	27	26	29
Gender	13/14	18/9	11/16	11/16	12/16
average age	51.74	52.85	52.62	51.85	51.85
Iron (µmol/l)	15.36 ± 0.71^{a}	13.23 ± 0.78 ^{b}	10.63 ± 0.65^{c}	10.52 ± 0.79^{c}	9.48 ± 0.62^{c}
Ferritin (ng/ml)	223.44 ± 26.51^{c}	322.06 ± 49.13 ^{bc}	318.55 ± 62.77 ^{bc}	421.73 ± 54.44^{b}	644.04 ± 77.55^{a}

The synthesis of Hgb requires iron. As a result, patients should undergo a thorough assessment to determine their iron availability, which should involve evaluating their TIBC and serum iron. The quantity of iron that is immediately available for hemoglobin production is reflected in the serum iron and the % TSAT. The body's entire iron stores are reflected in serum ferritin. If one of these indices is low, it can mean that extra iron is required to maintain erythropoiesis.

In young, healthy people, seminal erythrocytes are typically responsible for maintaining iron production and homeostasis. As these cells age and deteriorate, iron released from them is transported to bone marrow through the reticuloendothelial system (RES), in which it is easily absorbed into bone marrow and is combined to the erythroblasts. Furthermore, homeostasis of normal iron is balanced and maintained with the aid of (23) the iron absorption process from daily dietary intake provided to the human's body and after that this iron is stored and conveyed to bone marrow for additional processing. Nevertheless, in dialysis or chronic renal diseases, patients are often meant to undergo regular blood replacements, transfusions and filtrations in dialysis that is a great way of further loss of iron from patients. Additionally, there are some conditions in chronic renal diseases because of which there is iron malabsorption in patients' gastrointestinal tract. Therefore, there is often severe lack and loss of iron in CKD patients, that may also be called a natural iron deficiency that results in iron blockage from reaching to erythroblast production site. Even if iron is found in large amounts and stored in human's body in its respective reserves, it cannot reach the erythroblast production site because of reticuloendothelial cell iron's blockade (20,26,30).

In chronic renal diseases, very few studies revealed significant associations between high levels of serum ferritin and progression of renal diseases. It was indicated by Tsai et al. that CKD patients who showed S. ferritin levels > 288 ng/mL were more probably to develop adverse renal outcomes in comparison with individuals with S. ferritin levels < 132 ng/Ml (39).

According to instructions of the World Health Organization, it was stated that in non-healthy adult people, S. ferritin concentrations > 500 ng/mL may suggest an iron overload risk (30). Levels of S. ferritin in the range of (200–2,000) ng/mL can be elevated because of non-iron related factors, such as malnutrition–inflammation complex syndrome elements, whereas very high levels of S. ferritin > 2,000 ng/mL normally indicate to iron overload CKD patients (8,31). In our current study, level of S. ferritin was high in stage 5 with dialysis (644.04 ±77.55[a)] ng/mL thus, the majority of participants may have iron-associated condition iron-overload.

Iron overload is a condition of continuous iron accumulation in the body, resulting in a challenge to the tissue storage system capability and may cause tissue and organ damage. In an autopsy study conducted by Ali et al. (40) on 50 patients on hemodialysis in the pre-EPO era, it was revealed that a surprisingly high numbers of individuals developed severe iron tissue overloads (36%) and demonstrated that S. ferritin level was not a very good predictor of iron overload degree. It is important to mention that even with the additional tissue iron, tissue pathology or damage was not evidenced. In their recent study, Canavese et al. (41) found that most of the 40 hemodialysis patients they studied developed intravenous iron discontinuity because of the high S. ferritin levels. They used the superconductive quantum interference device magnetic resonance imaging technology (SQUIDMRI), that examines tissue iron overload non-invasively. This technology was found to be well-correlated with iron load measurement from tissue specimens obtained by liver biopsies. It was reported by Canavese et al. (41) that 37.5% of patients developed severe iron overloads, which coincided with the findings of Ali et al. (36%). It is of interest that the risk of iron overload was not associated well with serum ferritin, treatment with intravenous iron, or intravenous iron dosage.

Table (4-3) Albumin and total protein levels in patients with renal failure compared to healthy people

Parameter		Renal failure			
	control	Stage 3	Stage 4	Sage 5 Without dialysis	Stage 5 with dialysis
	Group (1)	Group (2)	Group (3)	Group (4)	Group (5)
Numbers	27	27	27	27	28
Gender	13/14	18/9	11/16	11/16	12/16

average age	51.74	52.85	52.62	51.85	51.85
Albumins (g/dl)	4.60 ± 0.08[a]	4.04 ± 0.16 b	4.15 ± 0.10 [b]	4.18 ± 0.13 [b]	3.35 ± 0.10 c
Total protein (g/dl)	6.49 ± 0.15 [abc]	6.12 ± 0.24 [c]	.78 ± 0.18 ab	6.29 ± 0.18 [bc]	.0 ± 0.17 [a]

In healthy individuals, serum albumin levels are kept within specific ranges. Reduced albumin levels are a strong predictor of CVD and cause mortality in HD patients, and they predict mortality in all populations. Our findings agreed with those of other studies performed on kidney failure patients, and showed decreased albumin levels in CRD patients in comparison with the control group. Other studies also revealed that low serum albumin levels independently related to a decline in renal functions in older people, who were (70-79) years old. The blood concentrations of albumin were also significantly related to kidney functions and proteinuria [24]. The blood levels of albumin are significantly related to the renal glomeruli deterioration in comparison with the healthy controls and the highly risk of last stage of chronic renal disease progression, in addition to the low blood albumin levels was related to high probability of rapid deterioration in renal functions and elevated acute and chronic renal disease risks [23].

Albumin is a negative acute phase protein (10). Hypoalbuminemia patients in HD have higher amounts of acute-phase proteins and decreased albumin synthesis (11). We examined cross-sectionally (12) and longitudinally in HD patients the association between S. albumin levels and cytokines, or levels of acute phase protein, in addition to normalized protein catabolic rate (nPCR). Cross-sectionally, albumin levels were negatively linked with cytokines that regulate acute phase responses, e.g. interleukin-6 (IL-6), or indicators of acute inflammations, such as C-reactive protein (CRP) (14). Furthermore, there was an inverse correlation between albumin concentration and nPCR, indicating a relationship between serum albumin levels and dietary protein13. Interestingly, CRP concentrations have not predicted future serum albumin levels, while having a strong correlation with contemporaneous serum albumin values (13, 15)

Conclusions:

According to the current study findings, both erythropoietin and ferritin can be utilized as kidney failure indicators. In addition, albumin and total proteins were found to be the most significant indicators for renal function detection.

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