

The Role of Erythropoietin Hormone and RAAS In Chronic Renal Disease

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Abstract: Patients with chronic renal disease (CRD) have altered levels of erythropoietin (EPO), which plays an important role in the process of erythropoiesis. The aim of this study was to measure EPO levels in individuals suffering from (CRD) and compare these levels with a healthy control group, taking into account GFR, and the RAAS system (Renin, angiotensin, Aldosterone). The results show that EPO concentration is significantly lower in EPO patients (7.29 ± 2.67 mIU/ml) than in the control group and its members (11.45 ± 4.07 mIU/ml, $p < 0.001$). EPO levels also decreased significantly in the lower GFR stages of patients with deteriorating renal function. In addition, it is hypothesized that the inverse effect of EPO and the components of the RAAS (renin, ANG II, and ADH) is indicative of regulation. The highlight of this research is how undiagnosed RAAS abnormalities and renal impairment are associated with EPO synthesis deficiency. This adds to the challenge of providing appropriate treatment for patients with CRD.

Keywords: erythropoiesis, RAAS abnormalities, GFR, Renal function

INTRODUCTION

Erythropoietin is a key producer of oxygen homeostasis, especially in conditions of anemia, such as high altitude and strenuous exercise, as well as having many clinical uses (management of anemia associated with chronic renal disease, cancer therapies, etc. ¹. Knowledge of the pathways and functions of erythropoietin is fundamental both medical research and to therapeutic therapies ²⁻³. the renin-angiotensin-aldosterone system (RAAS) is a critical manager of blood volume, electrolyte homeostasis and systemic vascular resistance ⁴. The RAAS is responsible for acute and chronic adaptations, while the baroreceptor reflex is activated in the short term to a decrease in arterial pressure ⁵⁻⁶. The classical concept of RAAS consists of three keys substances: aldosterone, renin and angiotensin II ⁷⁻⁸. Three substances (angiotensin II, aldosterone, and Renin) are raised, when renal blood pressure decreases, when salt is already on the distal convoluted tubule, or when high beta-agonism occurs, leading to increased arterial pressure; nonetheless, despite the expansion of knowledge on trying to open out new components of the systemic array over the previous few decades from the RAAS ⁹.

Glomerular filtration rate (GFR) is the most common measure of kidney function; it is defined as the volume of plasma that passes from the glomerulus into Bowman's space per unit of time—in people, this is approximately 1.0 to 1.1 liters per minute, or 20% to 25% of cardiac output can flow through the kidneys ¹⁰⁻¹¹. The afferent arteriole leads blood into single glomerular tufts, followed by the efferent arteriole, which carries blood out ¹²⁻¹³.

METHODOLOGY

One hundred samples were collected from people with CKD in the early stages of the disease and 80 samples from apparently healthy people of both sexes at the Nephrology Hospital in Dohuk

Governorate, Iraq after taking the official approval (Research Ethics Committee) at the Dohuk Health Presidency (31072024-6-8) dated July 31, 2024. Then the level Hormonal (erythropoietin, aldosterone, angiotensin II), and renin enzyme were measured by ELISA kits from BT-LAB and Sunlong (China) and Diametra (Italy) in the blood serum of both groups of patients and healthy people. Data were analyzed using SPSS (version 27). Analysis of variance (ANOVA) was used to compare the means and standard deviation between the two groups. Independent samples t-test was used to analyze the differences between the two groups. Results were considered statistically significant when the p-value was less than 0.05. 95% confidence intervals were calculated to determine the accuracy of the estimates.

RESULTS AND DISCUSSION

Determination of the normal level of Erythropoietin hormone in healthy people:

Since there were no previous studies to determine the normal human erythropoietin (EPO) hormone level in healthy controls and both sexes, it was examined for the first time as a marker of the normal range of the hormone, as shown in Table (4-1) to be used as a reference in comparing the range of variability in its level in disease conditions, such as in the current study of CKD. It also showed that the level of hormones in males is higher compared to females, perhaps due to the hormone testosterone, which provokes the kidney to secrete erythropoietin.

Table (4-1): Determination of the normal level of Erythropoietin hormone in healthy people

Normal Concentration of Erythropoietin (EPO) in Human	
Male Normal Range (mU/ml)	8.06 – 16.82
Female Normal Range (mU/ml)	6.93 – 14.21

Erythropoietin & RAAS system variables for patients with chronic renal disease compared to the control group and for both sexes:

Table (4-2) represents the comparison of EPO and RAAS parameters in controls and chronic renal disease patients. In chronic renal disease patients, EPO level is statistically significantly ($p < 0.001$) lower (7.29 ± 2.67) than in the controls (11.45 ± 4.07) with confidence range of (-5.62 to -2.71). Reduced erythropoietin in patients with CKD is caused by declining kidney function as the disease progresses, very compromised kidneys do not release adequate amounts of erythropoietin even when blood oxygen levels are low.¹⁴⁻¹⁵ This means fewer red blood cells are manufactured in the bone marrow, causing anemia. Besides, the present chronic inflammation in the majority of cases of nephropathy has the potential to cause reduced bone marrow response to erythropoietin.¹⁶ In the case of Renin, Angiotensin II (ANG II), and Aldosterone Hormone (ADH) patients with chronic renal disease have higher (49.73 ± 10.97) concentrations than control (25.58 ± 7.15) with a high confidence interval of 10.74 to 19.03. The concentration of ANG II is also very high in patients (31.04 ± 10.5 vs. 16.15

± 7.2) with a confidence range of 20.07 to 28.21. The highest difference is observed in ADH, where patients with chronic renal disease have 127.86 ± 43.20 instead of 46.69 ± 19.45 for the controls with confidence interval of 65.73 to 96.61. The statistical significance of the parameters is shown by

low (<0.001) p-values and indicate a high association between chronic renal disease and hormonal and enzymatic changes. Previous studies indicate that the Renin-Angiotensin Aldosterone System (RAAS) activation in chronic nephropathy is a physiological response trying to keep the blood pressure and renal filtration efficiency at close to the normal levels, but as the disease advances, the excessive amount of the said activation, the blood pressure, sodium and water retention, and cardiovascular risk all rise up¹⁷⁻¹⁸.

Table (4.2): Erythropoietin &RAAS system variables for patients with chronic renal disease compared to the control group and for both sexes

Variables	Chronic Renal Disease Patients (Mean $\pm$ SD)	Control Group (Mean $\pm$ SD)	p-value	95% Confidence Interval of the Difference	
				Lower	Upper
EPO (mU/ml)	7.29 $\pm$ 2.67	11.45 $\pm$ 4.07	$<0.001^{***}$	-5.62	-2.71
Renin (pg/ml)	49.73 $\pm$ 10.97	25.58 $\pm$ 7.15	$<0.001^{***}$	10.74	19.03
ANG II (pg/ml)	31.04 $\pm$ 10.5	16.15 $\pm$ 7.2	$<0.001^{***}$	20.07	28.21
ADH (pg/ml)	127.86 $\pm$ 43.20	46.69 $\pm$ 9.45	$<0.001^{***}$	65.73	96.61

Erythropoietin hormone level for patients with chronic renal disease based on GFR stages:

Table (4-3) shows high correlation between the severity of serum erythropoietin and glomerular filtration rate in the patients with chronic nephropathy and this correlation is linear, and as per analysis conducted shown proved that the patients who have the first stage (GFR ≤ 90 mL/min) have an extremely high degree of erythropoietin of (11.45 $\pm$ 4.06) mIU/ml identical to the control group. With increasing age to the second stage (GFR 60-89 mL/min) the hormone starts to decrease to (7.20 $\pm$ 2.70) mIU/ml, while during the third stage (GFR 30-59 mL/min), the content of the hormone also drops further to (6.32 $\pm$ 1.23) mIU/ml. Statistical processing indicates that the reduction in the contents of erythropoietin in the initial stages is statistically significant as P-value (<0.001). This may be due to the decreased ability of renal cells to secrete erythropoietin and the inflammation of the renal tissue to secrete substances that stimulate the production of the hormone, thus causing a deficiency in the body.¹⁹⁻²⁰

Table (4.3): Erythropoietin hormone level for patients with chronic renal disease based on GFR stages

Correlation of erythropoietin hormone with RAAS system variables in patients with chronic renal

	Stages	EPO (mIU/ml) Mean±SD	p-value
GFR (mL/min)	Stage.1 (≥ 90)	11.45 ± 4.06	<0.001***
	Stage.2 (60-89)	7.20 ± 2.70	
	Stage.3 (30-59)	6.32 ± 1.23	

disease:

The results shown in Table (4-4) for both sexes demonstrated a strong correlation between Chronic renal disease and low erythropoietin, which confirms that this hormone can be considered as a diagnostic marker for CRD. The table indicates that there is a very strong inverse Pearson's correlation for both sexes between erythropoietin and both Renin, angiotensin II, testosterone (RAAS). This is because a decrease in the level of erythropoietin means that kidney function has deteriorated and leads to activation of the RAAS; And Then renin enzyme secreted from the kidneys converts angiotensin to angiotensin I, which in turn is converted to angiotensin II by angiotensin- converting enzyme (ACE).^{21 - 22-23} The activation of ACE leads to increased renin secretion, which ultimately leads to higher plasma concentrations of angiotensin II in the circulation, leading to glomerular damage and hypertension, and angiotensin II promotes vasoconstriction in the lungs, which leads to glomerular damage and hypertension, and angiotensin II promotes vasoconstriction of the blood vessels, cardiac hyperactivity, inflammation, and wound fibrosis.²⁴⁻²⁵

Table (4-4): Correlation of erythropoietin hormone with RAAS system variables in patients with chronic renal disease.

RAAS Variables	Female	P-value	Male	P-value
	Pearson Correlation		Pearson Correlation	
Renin (pg/ml)	-0.685	0.002	-0.587	<0.001
ANG II (pg/ml)	-0.762	<0.001	-0.846	<0.001
ADH (pg/ml)	-0.860	<0.001	-0.736	<0.001

CONCLUSIONS

In this study, erythropoietin (EPO) levels are much lower in patients with chronic renal disease (CRD) than normal subjects. The greatest fall in EPO is seen in patients with a lower glomerular filtration rate (GFR), demonstrating a relationship between a reduction renal function and decreased EPO production. What the study really highlights as well as comes out of it is related to identifying problems in this system that are called renin angiotensin aldosterone system, or RAAS. This system

includes renin, angiotensin II, and aldosterone. This shows it's very important that people who have chronic renal disease also get checked earlier for dysregulation of their RAAS system. This can help greatly by reducing EPO shortages, which in turn improves medical options.

SUPPLEMENTARY MATERIAL

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