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Effect of Some Antioxidants and Biochemical Parameters on Iraqi Patients Undergoing Regularly Peritoneal Dialysis

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Abstract: Increased free radical species is one of the most prevalent problems in patients with chronic renal failure (CRF) receiving peritoneal dialysis (PD), which causes a variety of biochemical abnormalities, including anemia. The present research aimed at contrasting the actions of antioxidants such as superoxide dismutase (SOD), paraoxonase (PON1), and ferritin levels with oxidative stress markers such as malondialdehyde (MDA), nitric oxide (NO), and uric acid (UA), as well as levels of some biochemical variants such as blood glucose, blood urea (BU), creatinine (Cr), erythropoietin (EPO), hemoglobin (Hb), iron (Fe), and total iron binding capacity (TIBC), while body mass index (BMI) and creatinine clearance (CrCl) were calculated. The 124 participants in this study were included; 64 patients with CRF under PD, and 60 apparently healthy subjects, sex/age-matched representing the control group.

This study found a substantial drop ($P < 0.05$) in PON1 and SOD activity, as well as levels of Hb, Fe, TIBC, EPO, and CrCl levels in PD patients versus healthy controls. Patients showed significantly higher amounts of serum ferritin, BU, sCr, MDA, NO, UA, and BU/sCr ratio compared with controls ($P < 0.05$). The results

showed a substantial increase (P<0.05) in the blood glucose level. Conclusion: Serum paraoxonase PON -1 activity is more typically altered than other biochemical markers in peritoneal dialysis patients. Anemia is a common and frequently early consequence of chronic kidney disorders.

Key words: Chronic renal failure; Peritoneal dialysis; Antioxidants; Oxidative stress; Anemia.

Aim of this study: To evaluate the role of some antioxidants, oxidative stress markers as well as levels of some biochemical variants in peritoneal dialysis (PD) and the correlation analysis between the studied parameters in this patients group.

Introduction

Chronic renal failure (CRF) is the end stage of long-term kidney illness. This occurs when kidney functions fail to meet the needs of the body. Dialysis will be required when just 10% to 15% of renal function is left [1]. The two methods of dialysis are hemodialysis and peritoneal dialysis, respectively. Both kinds accomplish the traditional function of failing kidneys, which is to filter waste or extra substances from the blood [2]. The most frequent therapy for CRF is hemodialysis (HD), which is the normal technique to eliminate uremic substances (UTs) from the body [3].

PD is a replacement treatment of the kidneys that removes waste and excess fluid from the circulation and is one of several renal replacement therapies available to those who have end-stage renal failure [4]. It involves inserting a soft, hollow tube (catheter) into the intestines and filling it with dialysis fluid. The solution contains a form of glucose that eliminates waste and excess fluids. Wastes and fluids leave the blood vessels, travel along the peritoneum, and enter the solution. After a certain amount of time, the solution of water and trash is extracted and disposed away [5].

Kidney diseases, which commonly cause a decrease in glomerular filtration rate (GFR) and increased urea and creatinine levels, eventually lead to chronic renal failure (CRF) [6]. The glomerular filtration rate (GFR) influences CRF diagnosis, staging, and survival [7]. CRF is connected with elevated levels of some metabolic markers while decreasing others. Free radicals are becoming increasingly frequent in CRF variations.

Free radicals, can be created by numerous endogenous mechanisms, such as activating immune cells and mitochondrial respiration, as well as by external sources, such as radiation, pollutants, and smoking. These free radicals induce oxidative stress (OS), which is connected to the development of chronic illnesses such as CRF [8].

Oxidative stress (OS) is a critical factor in defining the status of continuing inflammation in CRF patients on peritoneal dialysis (PD). While antioxidants are a promising alternative for preventing OS in PD patients while preserving peritoneal function [9]. MDA, NO, and UA were utilized in this investigation to measure oxidative stress. Malondialdehyde (MDA) is a common OS marker in various studies.Under normal conditions, MDA, a water-soluble and low molecular weight (Mwt), is largely removed in the urine. However, it is unknown how much MDA is removed by the kidney [10].

Oxidative stress (OS) can cause the kidneys to produce more vasoconstrictor molecules and retain more sodium. The second OS used in this investigation is NO, which influences renal

blood stream, tubuloglomerular feedback (TGF), and pressure natriuresis [11]. Every day, uric acid is removed from the body through the kidneys. Because the human body lacks the uricase enzyme, uric acid cannot be converted to the more soluble compound allantoin[12].

The bulk of serum uric acid (UA) is freely filtered in the renal glomeruli, and roughly 90% of filtered uric acid is reabsorbed, indicating that it plays a significant physiological role [13]. Uric acid scavenges peroxides, serves as an antioxidant, and produces potent reactive oxygen species (ROS). Uric acid is readily visible in the cytoplasm of most human and mammalian cells, including the liver, vascular cells, endothelial cells, and human nasal secretions, where it acts as an antioxidant [14].

Enzymatic antioxidants are a type of enzyme that reduces the effects of oxygen toxicity by preventing it from producing free radicals or oxidizing molecules, thereby playing a vital role in protecting cells from oxidative stress [15,16]. Some antioxidants include superoxide dismutase (SOD), paraoxonase (PON1), and ferritin.

Iron is required for several biological processes, including heme synthesis, mitochondrial respiration, DNA synthesis, iron-dependent catalytic reactions, oxygen transport, and energy production. Inadequate or high body iron levels are linked to a variety of undesirable outcomes (17). Iron deficiency, on the other hand, has a deleterious clinical impact through both hematological and nonhematopoietic mechanisms (18). Serum ferritin is routinely used in clinical practice to determine iron storage. Furthermore, kidney failure can affect hormone production, specifically erythropoietin (EPO). EPO is an essential hormone for erythrocyte synthesis, hence persons with end-stage renal disease (ESRD) frequently develop anemia [19].

In addition to a shortage of EPO, shorter erythrocyte lifespan has been regarded one of the contributing factors to anemia in people with ESRD [20]. Anemia is a prevalent disease in persons with chronic kidney failure (CKD), and it has been associated to poor outcomes [21]. If left untreated, CKD-related anemia causes a number of problems, including decreased oxygen release and usage in tissues, increased cardiac output, and an expanded heart region. Peritoneal dialysis, or PD, is currently the preferred kidney replacement treatment for over 130,000 patients globally, accounting for around 15% of the overall dialysis population [22].

Materials and methods

Subjects

The present study included 60 patients (32 males and 28 females) with chronic renal failure (CKD) undergoing peritoneal dialysis (PD) attending the dialysis unit of Kirkuk Teaching Hospital in Iraq , compared with equal numbers of apparently healthy volunteers (30 males and 30 females) aged (20-70) years for both patients and controls. The mean age was (47.95 ± 15.69) years for patients and (46.11 ± 14.69) years for apparently healthy controls.

Exclusion Criteria

Patients with diabetes mellitus. A previous history of intravenous iron therapy. Hypertension..

Alzheimer's Disease and Vascular Dementia, Hepatitis.

Samples and sampling

5 of venous blood was drawn from the arm of both patient and apparently healthy control, left to clot, and then separated in a centrifuge at 3500 rpm for 10 minutes. The serum was then divided into 4 parts using Eppendorf tubes to avoid freezing and thawing and stored at -20°C until the biochemical tests included in the study were performed.

Determination of BMI

The BMI was calculated according to the equation(13): BMI= weight (kg) / (height in meter) ^{2} (23).

Determination of CrCl

The value of creatinine clearance (CrCl) was evaluated from the creatinine concentration in the collected urine sample (UCr), the volume of the collected urine (usually for 24 hours) and the plasma concentration (PCr) by the following equation[37]:

$$CrCl = \frac{Cr \times 24\text{-hour volume}}{PCr \times 24\ hour \times 60\ min} \quad (24).$$

Parameters analysis:

Biochemical parameters information used in this study with their suppliers are summarized in Table 1(1).

Table (1): Methods of testing the biochemical parameters.

No.	Biochemical parameters	method
1	Urea	modified urease- berthelot method (25)
2	Uric acid	Uricase method (26)
3	Creatinine	Colorimetric kinetic method without deproteinization. (27)
4	MDA	human enzyme-linked immunosorbent assay kits Catalog No. CSBA082431
5	NO	Human Nitric oxide (A012) ELISA Kit
6	PON1	Mackness, M. method (29)
7	Hb	Quantitative determination of Hemoglobin (colorimetric method) (30)
8	Fe	Colorimetric method (31)
9	TIBC	Colorimetric method (32)
10	Ferritin	Enzyme Linked Florescent Assay (ELFA) (33)
11	EPO	ELISA Kit (MBS163739)

Statistical Analysis

All information were analytically evaluated with SPSS version 26 for Windows. The differences between groups were analyzed statistically using one-way ANOVA and the ANOVA test. Descriptive data were expressed as mean ± SD values. Significant differences were defined as p-values < 0.05.
All data will be shown as mean ± SD. The data was analyzed using the student t-test. Pearson correlation was utilized to calculate the correlation coefficient between the markers under study.

Results

The research data were separated into two groups: patients (G1) and seemingly healthy controls (G2). The baseline and demographic features of the present study population are summarized in Table 1. There was no significant difference between the patients and the controls in terms of age and BMI. The average HD treatment duration for CRF patients in the current study was 1.80 ± 0.23 years. In the current study, blood urea and serum creatinine concentrations increased significantly in CRF patients as compared to controls.

Table (1): The socioeconomic features of the studied group.

Characteristics	G1	G2
Age (years) (mean ± SD) (Min. - Max.)	47.95 ± 15.69 ** (20 – 70)	45.68 ± 14.44** (20 – 70)
Sex males females Total	 32 28 60	 30 30 60
BMI (Kg/m²)(mean ± SD) (Min. - Max.)	27.74 ± 1.61** (26 - 33)	25.72 ± 1.49** (21 – 27)
Duration of PD (Years)(mean ± SD)	1.80 ± 0.23	

**P > 0.05 not significant

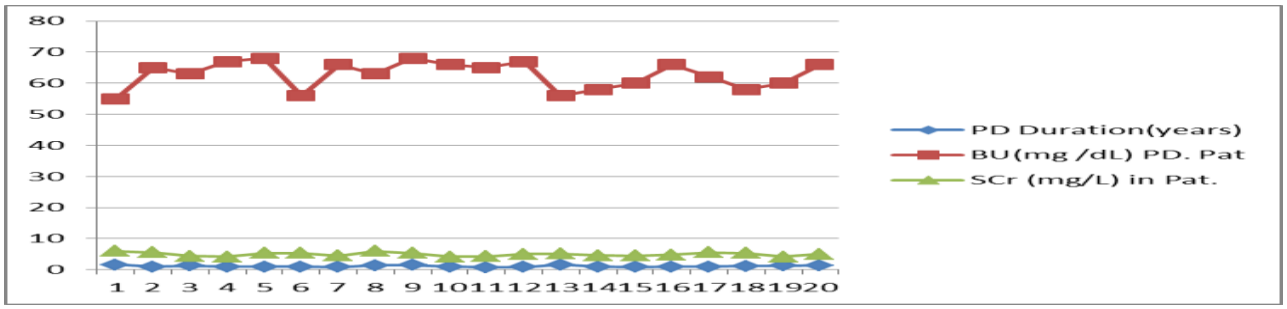

Figure (1): The demographic characteristics of the study population

Table (2): Markers of renal impairment function tests (BU, SCr, CrCl), oxidative stress (MDA, UA, NO) and antioxidants (PON1, SODin Patients of PD and apparently healthy control.

Parameters	G1 (mean ± SD) n= 60	Median (mini-max)	G2 (mean ± SD) n= 60	Median (mini-max)
BU (mg/dl)	65.36 ± 4.82*	66 (55 - 78)	25.49 ± 1.56	25.3 (21.5 – 28.1)
SCr (mg/dL)	4.89 ± 0.64*	5 (3.5 – 6.5)	0.81 ± 0.16	0.83 (0.5 – 1.2)
CrCl (ml/min)	58.83 ± 3.90*	59 (49 - 68)	118.90 ± 8.13	121 (100.00 - 128.00)
BU/SCr				
MDA (µg/ml)	5.47 ± 0.51*	5.40 (4.6 – 6.6)	2.85 ± 0.34	2.9 (1.8 – 3.2)
Uric acid mg\dl	6.85 ± 0.60	5.8 (8 - 6.9)	4.06 ± 0.67	2 (5.1 – 4.2)
NO (µmol /L)	134.11 ± 7.75*	135 (115 - 148)	69.27 ± 5.72	70 (55 – 77)
PON1 (IU / L)	54.50 ± 8.75*	55 (34-68)	157.73 ± 8.70	159(173 - 134)
Superoxide dismutase SOD (U\L)	5.36 ± 0.93*	5.3 (3.7 – 7.3)	10.09 ± 1.39	15 (11.6 – 17.1)

* Significant at P ≤ 0.05

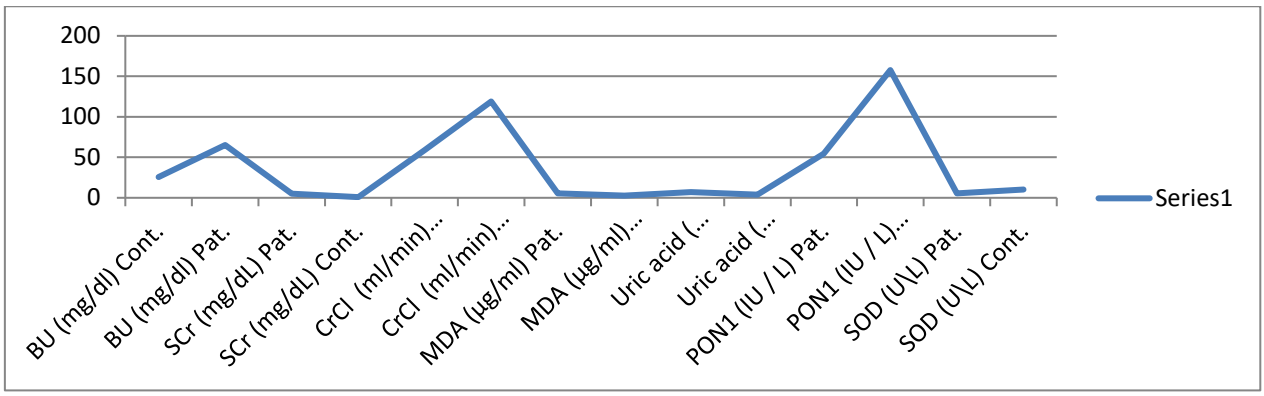

Figure (2): Markers of renal impairment function tests (BU, SCr, CrCl), oxidative stress (MDA, UA, NO) and antioxidants (PON1, SODin Patients of PD and apparently healthy control.

Table (3): Some biochemical parameters in the peritoneal dialysis (PD) patients in comparison to apparently healthy control.

Parameters	G1 (mean ± SD) n= 60	Median (mini-max)	G2 (mean ± SD) n= 60	Median (mini-max)
Hb (gm/dl)	10.30 ± 0.86*	10.4 (7.8 – 11,7)	13.38 ± 0.73	13.4 (12 - 15)
Fe (µmol/L)	8.94 ± 1.45*	8.9 (5.8 - 11.4)	21.67 ± 1.22	21.7 (17.6 - 24)
TIBC (µmol/L)	33.80 ± 2.83*	34 (28 - 39)	57.13 ± 3.52	58 (48 - 63)
Ferritin (ng/ml)	330.33 ± 53.26 *	330 (238 -240)	101.22 ± 7.27	101 (86 - 110)
Erythropoietin EPO (IU/mL)	6.76 ± 0.82*	6.9 (5.10 - 8.30)	13 ± 0.88	12.9 (11.5 - 14.9)

* Significant at P ≤0.05

Table (4): Correlation coefficient (rho) among some of the studied variables in patients under PD.

Variables	Correlation coefficient (rho)	P
BU VS CrCl	- 0.37	0.020
Serum Cr VS CrCl	- 0.61	0.001
BU VS PON1	- 0.510	0.001
Serum Cr VS PON1	- 0.921	0.000
BU VS MDA	0.41	0.010
Serum Cr VS MDA	0.653	0.001
BU VS NO	0.410	0.010
Serum Cr VS NO	0.661	0.001
BU VS UA	0.141	0.050
Serum Cr VS UA	0.213	0.031
BU VS SOD	- 0.220	0.010
Serum Cr VS SOD	- 0.782	0.000
BU VS EPO	- 0.046	0.740
Serum Cr VS EPO	-0.247	0.079
BU VS Fe	-0.092	0.090
Serum Cr VS Fe	-0.125	0.062
BU VS ferritin	-0.088	0.083
Serum Cr VS ferritin	-0.170	0.091

Discussions:

Measuring kidney function is one of the necessary tests to confirm the presence of kidney diseases in the samples under study. The outcomes demonstrated an increase in the level of urea, creatinine, and uric acid in the blood serum of individuals with kidney illnesses of both sexes at a probability threshold of ($p \leq 0.05$) when compared to healthy control individuals.

This is because urea is a less harmful metabolic product than ammonia, which is produced during protein metabolism in the urea cycle. It affects dietary habits and the condition of the kidneys, and is a highly sensitive indication of changes in hemodynamics including the perfusion of the kidneys. Elevated urea levels have been found to be closely linked with mortality in patients with heart failure (24).

Jiang Haijing also discovered that excessive urea levels may be connected with an increased risk of cardiovascular disease in the Chinese population (25). High urea levels are also considered a marker of urea retention in patients with chronic kidney disease. However, a number of recent experimental data indicate that urea is toxic at concentrations representative of chronic kidney disease.

The results also showed an increase in uric acid levels in the blood serum of patients with kidney disease of both sexes at a probability level of ($p \leq 0.05$) compared to healthy control subjects,. Hyperuricemia is a risk factor for all-cause mortality and cardiovascular disease. Another study used the average initial and final blood uric acid levels to determine the status of hyperuricemia, as hyperuricemia was a significant predictor of accelerated decline in glomerular filtration rate (eGFR) in chronic kidney disease and glomerular filtration rate (eGFR). Based on studies, uric acid is an appropriate biomarker for tracking the course of chronic renal disease and/or the efficacy of dialysis. This has been shown not only in older individuals, but also in youngsters, with Bibi (26) demonstrating a 22% drop in mouth uric acid content after dialysis.

Zvi-Ben (27) exhibited a 65% drop in uric acid content. The latter study, which included people who had end-stage renal disease and diabetes, found that uric acid levels jumped 8-fold (30-fold) among kids with chronic kidney disease when compared to the unaffected group. Uric acid values are closely related to serum uric acid concentration, but recent studies have shown that age and race are not related to salivary uric acid levels. However, males had approximately 40% higher serum uric acid concentrations, which were positively and significantly associated with BMI compared to females. Similarly, uric acid concentrations were elevated (28). Serum creatinine levels were also elevated in patients with kidney disease in both sexes, at a probability level of ($p \leq 0.05$) compared to healthy controls. This is consistent with what Dundar (29) showed that patients with a urea level higher than 23 mg/cm3, an albumin level lower than 5.3 g/cm3, and a creatinine level higher than 5.1 mg/100 cm3 in the emergency department had a higher risk of in-hospital death.

Measuring nitric oxide levels is an important criterion for assessing oxidative stress among groups. Our results showed a significant increase at the probability level ($p \leq 0.05$) in patients with kidney disease compared to healthy controls for both sexes. The affected male group recorded the highest levels compared to affected females. Oxidative stress damages kidney tissue and promotes inflammation, leading to further tissue injury and the accumulation of vulnerable biomolecules (30).

NO plays a role in many normal physiological functions as well as causing oxidative stress under pathologic situations. Studies have revealed that individuals with chronic kidney disease (CKD) have higher NO levels during an intermediate and pre-dialysis stages when compared to healthy controls. NO concentrations, on the other hand, are lower than those of patients with CKD on hemodialysis (31). Most surprisingly, salivary NO contents in patients having advanced kidney disease (ESRD) receiving dialysis treatment declined considerably. (32-33). The results we obtained are comparable with those of Zvi-Ben, who discovered a decline in the activity of the

enzyme SOD-superoxide dismutase and several endogenous antioxidant parameters in kidney patients. (34) The SOD enzyme also helps to reduce the damaging effects of nitric oxide on cells and the production of peroxynitric oxide. The study found a substantial decrease in catalase enzyme activity in individuals with renal illness ($p \leq 0.05$) in contrast to the control group. There were no differences reported between the sexes.

Overall, it is obvious that PON1 activity has prognostic and diagnostic relevance in CKD, as lower values imply impaired antioxidant defense as well as oxidant-antioxidant imbalance, both of which contribute to the etiology of cardiovascular risk. As a result, increasing PON1 expression and activity through nutritional and pharmacological approaches may constitute a promising therapeutic target for treating chronic kidney disease and slowing its progression. Nonetheless, it appears that large-scale, multicenter clinical trials are underway to determine the utility of PON1 activity as a biomarker. Furthermore, the significant variety in the selection of the substrates and the circumstances of the assay utilized with each substrate may lead to discrepancies in the comparison of values and the interpretation of the results.(35). In CKD patients, MDA, which is not excreted by the kidneys, alone accounts for high MDA concentrations, whereas fMDA and bMDA both contribute to MDA values in those on dialysis. The results of this study show that increased tMDA might be indicative not only in recent lipid peroxidation, but also of the necessity of evaluating free, bound, and total MDA among individuals with diminished kidney function in order to evaluate their oxidative status (36).

Anemia is a well-known complication of chronic kidney disease. The number of people with end-stage kidney disease, often known as ESKD, is rapidly increasing in Asia and around the world, presenting a huge financial burden on many governments. Iron and ESA supplements continue to be at the heart of anemia treatment. However, different governments' healthcare payment systems have a major impact on the overall prevalence of Parkinson's disease and the use of erythropoiesis-stimulating drugs (ESAs). A recent study of the French Language Peritoneal Dialysis Register from 2010 to 2017 revealed that 74% of 568 PD patients were treated with ESAs, 23% with oral iron, and only 11% with IV iron. (37) The average Hb level observed was approximately 12 g/dL. In this Asia Pacific locale, 82% to 96% of PD patients receive ESAs. Asia is a complex region with various ethnic groups, customs, and medical traditions. Common clinical practice recommendations suited to Asian countries and territories are critical because they account for the various socioeconomic systems. The advent of novel pharmaceutical treatments for anemia, particularly HIF-PHIs, will change the therapy options (38,39). There have been few large-scale placebo-controlled trials on the integration of iron in Parkinson's disease patients, and additional study is needed to determine the best method and amount of iron delivery in PD. With a rising number of persons getting dialysis in the Asian Pacific region, developing a kidney registry covering the entire may be beneficial for comparing epidemiologic data with clinical practice to improve anemia care in the PD community (40).

Conclusion

Serum paraoxonase PON-1 activity is more frequently altered in patients on peritoneal dialysis than other biochemical indicators. Anemia is a prevalent and often early side effect of chronic renal disease.

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