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EVALUATION OF COENZYME Q10 AND TOTAL ANTIOXIDANT CAPACITY IN SERA OF PATIENTS AGE 30-80 WITH RENAL FAILURE

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August 2021

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science

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ABSTRACT

EVALUATION OF COENZYME Q10 AND TOTAL ANTIOXIDANT CAPACITY IN SERA OF PATIENTS AGE 30-80 WITH RENAL FAILURE

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Master of Science in Chemistry

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This study was designed as a biochemical study of antioxidant and Q10 coenzyme using biomarkers and their role in laboratory diagnosis in a patient with renal failure. A group of 82 a sample with renal failure who were treated in Kirkuk State Hospital and 30 healthy samples aged between 30-80 years were included in the study. Samples were collected in the period 1/2 / 2021 - 30/4 / 2021. The samples were divided into two groups: Group I: patient: Group II: control. The study included measurement of some biochemical variables such as (Urea, Creatinine, Albumin, Cholesterol, Co enzyme Q10, Antioxidants). The results showed the following points, the mean level of urea and creatinine was increased (P = 0.0001), they were significant in the first group. The mean concentrations were (149.40a ± 39.53 mg/ dL and 6.57a ±2.32 mg/day). It doesn't matter in albumin and cholesterol. The mean concentrations were (3.99 a ± 0.40 mg/dL and 198.61 ± 36.81 mg/dL) compared to the control group, which showed (3.99a ± 0.40 mg/dL and 198.61 A ± 36.81 mg/dL. The study also showed a significant decreases in Coenzyme Q10 concentration level (P = 0.040) in patients with renal impairment aged 70-80 years, there was no significant change in the p-value of antioxidants at 0.813 (0.96b ± 0.43µL) when compared with control age.

2021, 69 pages

Keywords: Renal failure, Urea, Creatinine, Albumin, Cholesterol, Antioxidants, Coenzyme Q10

ÖZET

30- 60 YAŞ ARASI BÖBREK YETMEZLİĞİ OLAN HASTALARIN SERUMLARINDA KOENZİM Q10 VE TOPLAM ANTİOKSİDAN KAPASİTESİNİN DEĞERLENDİRİLMESİ

Harith Reja Jaseim AL-AKIDI

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Bu çalışma, böbrek yetmezliği olan bir hastada antioksidan ve Q10 koenziminin biyobelirteçler ve laboratuvar tanısındaki rolü kullanılarak biyokimyasal bir çalışması olarak tasarlanmıştır. Çalışmaya Kerkük Devlet Hastanesi'nde tedavi gören 82 böbrek yetmezliği olan 52 hasta ve yaşları (30 - 80) arasında 30 sağlıklı örnekten oluşan bir grup dahil edildi. Numuneler 1/2 / 2021 - 30/4 / 2021 döneminde toplanmıştır. Numuneler iki gruba ayrılmıştır: Grup I: hasta: Grup II: control Çalışma, (üre, kreatinin, albümin, kolesterol, Co anzim Q10, antioksidanlar) gibi bazı biyokimyasal değişkenlerin ölçülmesini içeriyordu. Sonuçlar aşağıdaki noktaları gösterdi: Ortalama bir konsantrasyon vardı Üre seviyesindeki ortalama artış ve kreatinin konsantrasyonu (P = 0,0001) birinci grupta anlamlıydı. Ortalama konsantrasyon ± SD (149,40a ± 39,53mg/dL ve 6,57a), albümin ve kolesterolde önemli değil. Ortalama konsantrasyon, ortalama ± SD (3,99a ± 0,40mg/dL) gösteren kontrol grubuna kıyasla ortalama ± SD (3,99a ± 0,40mg/dL ve 198,61 ± 36,81 mg/dL) idi (198,61 A ± 36,81 mg/dL). Çizelge 4,1 ve Şekil 4,1'de ve Çizelge 4,3 ve Şekil 4.3'te. Çizelge 4.5 ve Şekil 4.5'te gösterildiği gibi albumin. Konsantrasyonunda yaşa göre önemli bir değişiklik varken. Çalışma ayrıca 70-80 yaşlarında böbrek yetmezliği olan hastalarda Coanzim Q10 konsantrasyonu seviyesinde (P değeri 0,040) önemli bir düşüş gösterdi, ortalama ± SD (0,96 b ±0,43 µL) kontrol yaşı ile karşılaştırıldığında, antioksidanların p- değeri 0,813'te anlamlı bir değişiklik yoktu.

2021, 69 sayfa

Anahtar Kelimeler: Böbrek yetmezliği, Üre, Kreatinin, Albümin, Kolesterol ve antioksidanlar, Koenzim Q10

PREFACE AND ACKNOWLEDGEMENTS

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Harith Reja Jasim AL-AKIDI

Çankırı -2021

CONTENTS

LIST OF ABBREVIATIONS

%	Percent
±	Plus Minus
°C	Degrees Celsius
BMI	Body Mass Index
Ca^{++}	Calcium
CHOL	Cholesterol
CKD	Chronic Kidney Disease
Dk	Minute
EDTA	Ethylene Diaminetetraacetate
G	Gram
HB	Hemoglobin
HCT	Hematocrit
HDL	High Density Lipoprotein
Kg	Kilogram
LDL	Low Density Lipoprotein
LY	Lymphocytes
m^2	Square Meters
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mg	Milligram
mL	Milliliter
ng	Nano Gram
nm	Nanometer
PCT	Procalcitonin
PDW	Platelet Distribution Width.
PLT	Platelets
RBC	Red Blood Cell
RDWCV	Red Blood Cell Distribution Width
TG	Triglycerides
WBC	White Blood Cell
µg	Microgram
µL	Microliter

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1. INTRODUCTION

Renal failure is defined as the kidneys' inability to conduct excretory functions, resulting in the retention of nitrogenous waste products in the blood. The kidney's functions are as follows:

Volume and electrolyte regulation Nitrogenous waste excretion and exogenous chemicals, such as many medications, are eliminated. Synthesis of a wide range of hormones, including erythropoietin. Insulin, for example, is metabolized at a low molecular weight.

The two types of kidney failure are acute and chronic renal failure. As a result, renal failure develops when the kidneys are unable to efficiently clear waste products, causing waste materials and fluids to build up in the body (De Jong *et al.* 2008).

Acute Renal Failure (ARF): ARF is a syndrome with abrupt (hours-to-day) and generally reversible glomerular filtration. In 2012, AKI can be diagnosed as one of the following in accordance with the KDIGO criteria (Chertow *et al. 2005*), creatinine increase of 0.3 mg/ld in 48 hours (Hekimi *et al.* 2011), creatinine increase to 1.5 times baseline within last 7 days, or for 6 hours (Luo *et al.* 2014), urine volume must be less than 0.5 mL/kg per hour. Acute kidney injury (AKI) has recently supplanted acute renal failure (ARF) because AKI encompasses the complete clinical spectrum from a slight increase in blood creatinine to overt renal failure (Chertow *et al.* 2005). Chronic Renal Failure (CRF): Chronic renal failure (CKD) is defined as a persistent impairment of the kidneys that necessitates renal replacement therapy. The condition is known as end-stage renal disease (ESRD function, in other words, abnormally elevated serum creatinine for more than 3 months or a calculated glomerular filtration rate (GFR) of less than 60 mL per minute / $1.73m^2$. It usually involves a gradual decline of kidney function that necessitates the use of renal replacement medication (dialysis or transplantation) (De Jong *et al.* 2008).

CKD classified based on grade:

Grade 1: GFR greater than 90.

- Grade 2: 60 to 89
- Grade 3a: 45 to 59
- Grade 3b: 30 to 44
- Grade 4: 15 to 29
- Grade 5: Less than 15

The link between chronic renal disease and high uric acid levels: Increased uric acid levels have been linked to chronic renal disease in an independent manner (Kooman *et al.* 2003). It is hypothesized that insulin and the gastrointestinal tract share a two-way causal effect relationship, and thus type 2 diabetes is also associated with HU (Charra 2007). Moreover, obesity and dyslipidemia that are prominent components of metabolic syndrome share an association with uric acid level (Nashar and Fried 2012). Hypertension, diuretic use (thiazide) and obesity have been associated with a predisposition to increased uric acid levels as well as gout (Stone *et al.* 2019, Chen *et al.* 2007). Male sex showed a stronger association with uric acid level compared to females, especially in middle age (House *et al.* 2019). Even after understanding the. Aside from gouty arthritis, measuring SUA is not a common practice unless there are nonspecific and chronic musculoskeletal problems or an evident gout flare. As a result, it's possible that HU will go overlooked. Resistant hypertension and chronic renal dysfunction are two health risks associated with untreated and asymptomatic HU (Waller and Ramsay 1989). According to a systematic study published in 2015, population is a total of 24 countries have published evidence of HU prevalence. Asia, particularly East Asia, has a higher prevalence of HU; however, there is no evidence from South Asia (Wallace *et al.* 2004). A Bangladeshi study in 2018 estimated 9.3% of the population to be hyperuricemia (Raja *et al.* 2019). In India, the prevalence of HU estimated in 2018 was 25.8%, with an increased prevalence in diabetics, hypertensive, and diabetic hypertensive (Raja *et al.* 2019). A large-scale, national study has yet to be conducted in Pakistan. This study aims to contribute to the literature by determining the frequency of HU in a large metropolis in Southern Pakistan.

2. LITERATURE REVIEW

2.1 Diagnosis and Screening of HF in Kidney Transplant Recipients

All transplant candidates should have a screening echocardiogram to determine LV function, however there is little or no evidence that this is necessary. An echocardiogram is advised if there are signs of HF, a history of cardiovascular illness, or hemodynamic instability on dialysis. De novo HF in transplant recipients is treated in the same way that de novo HF in the general population is, with the exception of a check for coronary artery disease (House *et al.* 2019).

2.2 The Link between Chronic Renal Disease and High Uric Acid Levels

Increased uric acid levels have been independently associated to chronic renal illness (Zoppini *et al.* 2012). Insulin and the gastrointestinal tract are thought to have a two-way causal effect relationship, and hence type 2 diabetes is linked to HU (Rahman *et al.* 2020). Furthermore, obesity and dyslipidemia, both important components of metabolic syndrome, are linked to uric acid levels (Tani *et al.* 2020). Hypertension, diuretic use (Thiazide) and obesity have been associated with a predisposition to increased uric acid levels as well as gout (Gagliardi *et al.* 2009). Male sex showed a stronger association with uric acid level compared to females, especially in middle age (Gagliardi *et al.* 2009). Even after learning about the hallucinatory effects of SUA levels in conditions other than gouty arthritis, monitoring SUA is not a common procedure unless there are vague and chronic musculoskeletal aches or an obvious gout flare. As a result, HU may go unnoticed. Health hazards associated with undiagnosed and asymptomatic HU include resistant hypertension and chronic renal failure (Raja *et al.* 2019). According to a systematic study published in 2015, population-based evidence of HU prevalence has been published from 24 countries. A higher prevalence of HU has been recorded in Asia, particularly East Asia; however, there was no data from South Asia (Raja *et al.* 2019**)**. A Bangladeshi study in 2018 estimated 9.3% of the population to be hyperuricemia (Ali *et al.* 2018). In India, the prevalence of HU estimated in 2018 was 25.8%, with an increased prevalence in

diabetics, hypertensive, and diabetic hypertensive (Raja *et al.* 2019). In Pakistan, there is yet to be a large-scale, countrywide study. This study is an attempt to determine the prevalence of HU in the major metropolis in Southern Pakistan in order to contribute to the literature (Navekar *et al.* 2004).

2.3 Mechanisms of Hyperuricemia

The fact that hyperuricemia frequently precedes the onset of CRF suggests that mechanisms other than renal impairment are likely to play a role in the etiology of increased uric acid levels. According to research, a variety of strategies may be useful (Johnson *et al.* 2005). The most prevalent risk factors for CRF are obesity and metabolic syndrome, which are linked to hyperuricemia, which is caused by insulin resistance and the effects of insulin on urine excretion. High blood pressure is linked to narrowing of the renal arteries, which can result in uric acid retention. However, it has been proposed that elevated uric acid levels in the blood precede these disorders, therefore hyperuricemia may not be the fundamental cause. (Tsouli *et al.* 2006). Furthermore, one study discovered that uric acid rises to a minimum of secondary hypertension, a condition in which the renal arteries contract. Meat, sugar (fructose), and beer consumption are all known hyperuricemia risk factors (Ndrepepa 2018).

Fructose is an important candidate since it is linked to the development of metabolic syndrome in both animals and humans. Some studies suggest that fructose, one of the additional sugars, raises the risk of high blood pressure and kidney disease, but not all (Basciano *et al.* 2005). Fructose administration to rats reproduces the majority of the nephrotoxic effects of experimental hyperuricemia and may also cause kidney disease, which can be avoided by lowering uric acid levels. Blood uric acid levels can be raised by low-level lead and cadmium poisoning. Uric acid is most likely blocked by the kidneys. Low levels of lead in the blood were also linked to the development of CRF (Karamouzis *et al.* 2008). In chronic lead poisoning, nephrology is linked to the development of microvascular illness, glomerular sclerosis, and interstitial fibrosis, which are comparable to the symptoms of gout. Furthermore, giving lead to animals with CRF

is linked to the development of hyperuricemia and the progression of renal disease (Small *et al.* 2012). Allopurinol intake may lower systemic hypertension in these animals, although renal protection owing to toxicity caused by allopurinol and xanthine crystal deposition was not able to assess (Pacher *et al.* 2006). It's also feasible that meta-genetic factors play a role. Low birth weight, for example, is linked to elevated uric acid levels in the newborn's and mother's blood; this uric acid elevation lasts throughout infancy and adolescence and is linked to endothelial dysfunction and the development of hypertension. The cause of hyperuricemia is unknown, but genetic and family factors may play a role (Ikizler *et al.* 2018). It's also possible that genetic variables play a role. A mutation in uromodulin causes familial hyperuricemia (also known as medullary cystic kidney disease type 2) nephropathy, which is associated with progressive kidney disease and the development of glomerular sclerosis and interstitial fibrosis (Eckardt *et al.* 2015). At the time, some studies indicated that lowering uric acid levels had little effect on renal outcomes, while others reported that starting allopurinol treatment early improved renal results. It may be able to help prevent kidney damage in this case. According to a genome-wide investigation, uromodulin polymorphism has recently been related to the development of CRF in people. Surprisingly, hyperuricemia has recently been linked to a mutation in the uromodulin gene (Son *et al.* 2008). There is apparently a link between the UTP and the risk of gout, according to genome-level association studies. In the ARIC trial, the risk of developing gout in hypertensive patients was higher in those with polymorphisms in nephrogenic uric acid transporters that correspond with higher uric acid levels. A recent study on descendants of Ashkenazi Jews proved the importance of genetics in influencing the quantity of uric acid in the blood and its impact on the estimated glomerular filtration rate (eGFI) (Cameron and Simmonds *et al.* 2005).

2.4 Coenzyme Q10

Coenzyme Q10 (CoQ10), commonly known as ubiquinone, is a fat-soluble vitamin-like Quinone that has anti-oxidant properties. In mitochondria, CoQ10 transfers electrons from complexes 1 and 2 to complex 3 (Jankowski *et al.* 2016). CoQ10 treatment decreases superoxide production in endothelial cells and improves cardiac capacity in patients with heart failure (Belardinelli *et al.* 2006). Long-term CoQ10 therapy can minimize

significant adverse cardiovascular events and is considered safe and well-tolerated by the general public. (Mortensen *et al.* 2014) Patients with non-dialysis CKD and those undergoing dialysis have lower plasma CoQ10 concentrations (DiNicolantonio *et al.* 2015, Mehmetoglu *et al.* 2012).

When CoQ10 levels are low, electron transport is impaired, and reactive oxygen species are produced more frequently. CoQ10 supplementation may improve mitochondrial function and minimize oxidative stress in hemodialysis patients (Gazdikova *et al.* 2001, Nashar and Fried 2012). CoQ10 has the ability to prevent and treat cardiovascular disease, enhance heart function, and reduce oxidative stress in people with CKD. Although the results are still ambiguous, CoQ10 may have favorable effects on cardiac function, hypertension, glucose metabolism, lipid profiles, inflammation, and oxidative stress in patients with non-dialysis CKD and those getting dialysis. According to a recent meta-analysis, CoQ10 supplementation significantly improves the metabolic profile of people with CKD. (Bakhshayeshkaram *et al.* 2018). However, no systematic and comprehensive analysis of CoQ10's impact on cardiovascular events, inflammation, oxidative stress, glucose metabolism, and lipid profiles has been reported. The purpose of this systematic review is to evaluate the data regarding the effects of CoQ10 supplementation in people with chronic renal disease (Anavekar *et al.* 2004)

2.5 Antioxidant Function of CoQ10 in Plasma Lipoproteins

High levels of LDL, as well as smoking and hypertension, are thought to be key risk factors for cardiovascular disease. Experimental data has been developed demonstrating that oxidatively pass the endothelial cell lining and reach the subendothelial region, where they undergo oxidative damage. LDL that has been oxidatively damaged is capable of inducing additional processes, such as platelet activation, and exerts a chemotactic pull on circulating monocytes, causing them to migrate to the subendothelial region and become macrophages**.** Despite the fact that these cells contain low levels of the classical LDL receptor, they are able to take up oxidatively modified LDL more quickly, and this uptake is mediated by a distinct receptor known as the ‘‘scavenger receptor." As

previously mentioned, oxidatively changed LDL is rapidly detected by scavenger receptors? These events cause macrophages to accumulate lipids, primarily cholesterol and cholesterol esters, resulting in lipid-laden foam cells. The essence of the atheromatous lesions could be foam cells. LDL contains a number of lipid-soluble antioxidants that can prevent or reduce lipid peroxidation. CoQ10 plasma levels have been extensively studied (Van Gaal *et al.* 2006). The majority of plasma CoQ10 is carried by LDL, where it provides antioxidant defense alongside vitamin E. Although it is present in lesser concentrations than vitamin E, ubiquinol-10 can regenerate a-tocopherol from the tocopheril radical, making the vitamin E-ubiquinol pair the most important antioxidant mechanism in LDL. When compared to the same LDL in basal conditions, CoQ10 enriched LDL isolated from plasma of healthy individuals orally treated with CoQ10 for a few days were less sensitive to peroxidizability in vitro. BloodCoQ10 is mostly delivered via LDL, although it can also be found in other lipoproteins and blood cells. Micrograms per liter of plasma or micromoles per liter are the most common units of measurement. However, these figures should be normalized to the blood LDL content, or at the very least to plasma cholesterol levels. The ratio of CoQ10 to total cholesterol may be useful in predicting cardiovascular disease (Savalia *et al.* 2008). In addition to lowering LDL peroxidizability, CoQ10 may have a direct anti-atherosclerotic impact; in fact, animal studies have demonstrated that CoQ10 can reduce the risk of atherosclerosis (Is and Woodside 2001).

2.6 Coenzyme Q10 and Mitochondrial-Targeted Anti-Oxidants

When compared to other organs, the kidneys have the highest endogenous quantities of CoQ9 and CoQ10 (Small *et al.* 2012). This is most likely owing to the kidney's reliance on aerobic metabolism and high mitochondrial density. CoQ10 therapy is justified since it is critical to maintain endogenous CoQ10 levels in order to sustain mitochondrial health. Three distinct roles of CoQ10 have been identified: I electron transfer from complexes I and II to complex III through the inner mitochondrial membrane's ETC, followed by membrane polarization and ATP production (Small *et al.* 2012), (ii) the provident generation of O_2 - and H_2O_2; and (iii) the antioxidant quenching of free radicals

(Bocci 2006). CoQ10's main direct antioxidant role is to prevent lipid peroxidation, but it also has an indirect antioxidant role through its interactions with a-tocopherol (Singh *et al.* 2012).

Although the evidence for its efficacy is mixed, Ishikawa and colleagues found that a CoQ10 supplemented diet reduced kidney O_2 levels and enhanced renal function in hemi-nephrectomies mice. Although there are few human studies examining CoQ10 therapy for the treatment and/or prevention of CKD, CoQ10 levels decline with age 82, and identifying individuals with low CoQ10 levels may allow for targeted therapy with favorable outcomes. (Small *et al.* 2012).

2.7 Clinical Monitoring of CoQ10 Status

Although plasma measurements are commonly used in clinical monitoring of CoQ10 status, the level of circulatory CoQ10 is regulated by both food and circulatory lipoprotein status. It's unclear if plasma CoQ10 status mirrors that of other tissues and can be used as a proxy in this assessment. Although skeletal muscle is the tissue of preference for this assessment, alternative surrogates may be more appropriate to test renal CoQ10 status due to the possibility of tissue specific is enzymes in the CoQ10 biosynthesis pathway or a CoQ10 shortage being localized to a single organ (Pauly *et al.* 2014).

Due to the intrusive nature of a kidney biopsy, there are currently no studies that have examined the CoQ10 level of normal human renal tissue. Urinary tract CoQ10 analysis, on the other hand, could be a good way to measure kidney CoQ10 state and could fill a gap in the market for less invasive methods to identify tissue CoQ10 status. A new approach for measuring CoQ10 in urine was recently standardized, and reference values for a pediatric control population were established. This new urinary tract CoQ10 evaluation is a non-invasive approach that could be beneficial for evaluating CoQ10 kidney status for diagnosis and, more importantly, for monitoring CoQ10 treatment (Yubero and Larrañaga 2015).

This population could not be extrapolated from the findings of this study. Asymptomatic acute renal damage can occur in patients after they have been discharged from the hospital. Because the follow-up time in this study occurred throughout the patient's hospital stay, some cases may have been overlooked. Finally, additional research is needed on different CoQ10 doses and administration periods, as well as other AKI indicators including IL-18, KIM-1, L-FABP, and Cystatin-C (Dastan *et al.* 2020).

2.8 CoQ10 and Kidney Function in CKD

When compared to healthy controls, plasma CoQ10 levels in CKD patients (with or without hemodialysis) are considerably lower (Atakan *et al.* 2014, Xingjian *et al.* 2015). The source of this decrease in serum CoQ10 levels is unknown, however it could be linked to the increased oxidative stress seen in CKD patients (Oberg *et al.* 2004). May cause an increased degradation of CoQ10 (Cotán *et al.* 2011). Resulting in oxidative stress-induced degradation of CoQ10 synthesizing enzymes, potentially jeopardizing CoQ10 biosynthesis (Yubero and Larrañaga 2015). Furthermore, it has been postulated that the enzymes involved in CoQ10 production may be found in a super enzyme complex in mitochondria towards the inner mitochondrial membrane, close to MRC (Barros *et al.* 2005). A lack of MRC enzyme activity may thus affect the structural formation or function of the CoQ10 super enzyme complex, possibly as a result of increased ROS generation, which has been linked to MRC enzyme dysfunction. There is some evidence that CoQ10 supplementation may improve renal function and reduce the need for dialysis in patients with CKD. In a randomized, double-blind, placebo-controlled trial (Chang and Singh 2000).

Supplemental CoQ10 (3 x 100mg daily for 3 months) or placebo was administered to CKD patients. In both dialyzed and no dialyzed individuals, there was a significant improvement in indicators of renal function (e.g. serum creatinine) in CoQ10 supplemented patients compared to placebo. The number of patients requiring dialysis in the CoQ10-treated group reduced from 21 to 12, whereas the number of patients requiring dialysis in the placebo group remained similar at 24. The reduced form of CoQ10,

ubiquinol, was reported to lower kidney superoxide levels and improve renal failure in an animal model of CKD (Small *et al.* 2012).

Reduced CoQ10 levels may be a particular concern in CKD patients on cholesterol-lowering drugs called statins, as some studies have linked a CoQ10 deficiency to this pharmacotherapy in a subset of individuals. It has been postulated that these patients may have underlying mitochondrial illness, making them more vulnerable to the negative effects of statin medication (Smith *et al.* 2016). Statins are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, the rate limiting enzyme in cholesterol biosynthesis. Statins can also inhibit the body's production of coenzyme Q10 (CoQ10), which is synthesized via the same biochemical pathway as cholesterol (Sumida *et al.* 2020).

2.9 Statins and CoQ10

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which reduce mevalonate production, a critical metabolic step in the cholesterol manufacturing pathway. These powerful medications can cause a variety of muscle-related disorders known as myopathies. Different research has looked into the possibility of CoQ10 being an etiologic role in statin myopathy because the mevalonate pathway also leads to the manufacture of the isoprenoid side chain of coenzyme Q10. There is no doubt that statins lower plasma and leukocyte CoQ10 levels, and a few studies have also found that statin treatment lowers muscle CoQ10 levels. This contentious issue has been thoroughly studied. (Littarru and Langsjoen 2007). Small-sized, yet double-blind study also points out that CoQ10 exogenous administration reduced myopathy, symptoms in statin treated patients. Of course, a big double-blind scientific trial would be required to evaluate CoQ10's efficacy to reduce statin adverse effects (Case *et al.* 2007).

2.10 CoQ10 and Chronic Kidney Disease

Chronic kidney disease (CKD) is becoming more widely recognized as a global health issue. CVD-related mortality and morbidity are common in patients with CKD. CVD and its consequences are thought to be responsible for more than half of the mortality in dialysis patients with end-stage renal disease (ESRD) (Antoniou *et al.* 2018). Furthermore, we should note that the people who currently undergo dialysis or a kidney transplant to stay alive represent only 10% of those who genuinely require treatment to live (Couser *et al.* 2011, Bakhshayeshkaram *et al.* 2018, Kuchta *et al.* 2011). Moreover, CoQ10 levels are reduced in patients with CKD, showing that supplementation with this Quinone could be used as an antioxidant treatment in these patients. Several studies have looked into the effects of CoQ10 supplementation on metabolic profiles and oxidant/antioxidant status in CKD patients. In a meta-analysis carried out by (Firuzi *et al.* 2011), In terms of CoQ10's antioxidant characteristics, arandomized, double-blind, placebo-controlled research found that CoQ10 supplementation (120 mg/day) in CKD patients resulted in a reduction in the number of patients on dialysis after 28 days of treatment when compared to the placebo group. More recently, the results of a safety trial of oral CoQ10 supplementation in hemodialysis patients revealed a dose-dependent effect of CoQ10 in reducing oxidative stress, which increased mitochondrial function and reduced oxidative stress in hemodialysis patients (Parrado *et al.* 2018).

Daily supplementation with 1200 mg of CoQ10 was found to be safe and resulted in a reduction in plasma concentrations of F_2-isoprostanes, a marker of lipid oxidation, in patients on maintenance hemodialysis in a recent double-blind, parallel group, randomized clinical trial. Long-term CoQ10 supplementation improves kidney CoQ10 levels sufficiently to rescue hydrogen sulfide (H_2S) oxidation via raising sulfide: quinoa oxidoreductase (SQOR) levels, averting renal failure, according to animal studies (Gutierrez-Mariscal *et al.* 2020).

2.11 Antioxidant Systems

Oxidative stress is the imbalance between the rate of production and removal of produced oxidants. In other word it is an increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) and/or decrease in endogenous/exogenous antioxidants. It is the causative factor of a wide variety of diseases such as neurodegenerative diseases, diabetes, atherosclerosis, ischemia, and kidney disease (Rafieian-Kopaei 2013).

The hydroxyl radical (OH), superoxide anion (O^{-2}), hydrogen peroxide (H_2O_2), and hypochlorous acid are the most significant ROS molecules (Hecla). ROS molecules are extremely reactive and can cause harm to macromolecules including DNA, proteins, and lipids. Both endogenous and external sources create oxidant compounds. Oxidant enzymes, the auto-oxidation reaction, the mitochondrial electron transport chain, and phagocytes are all endogenous producers of ROS (Palipoch 2013). Xenobiotic, cigarettes and alcohols, radiations, chlorinated chemicals, and other exogenous ROS molecules were among them (Rafieian-Kopaei 2013). Nitric oxide produces RNS molecules as a by-product (NO). They, like ROS, serve an important role in sustaining numerous physiological activities, but high amounts can lead to a variety of clinical diseases. Peroxynitrite ($ONOO^-$), nitrite (NO^{-2}), and nitrate (NO^-) are the components of RNS molecules (NO_3). The body's defensive system (antioxidant system) fights ROS/RNS-caused damage (Rafieian-Kopaei 2013). Cellular damage was employed. Antioxidants are chemicals that can prevent substrates from oxidation (Halliwell 1996). Based on their mode of action, antioxidants are categorized as either breaking or preventive antioxidants. Preventive antioxidants can quench singlet oxygen and slow the start of chains by deactivating metals and decreasing hydro peroxides. Antioxidants that break the chain can either donate or receive an electron from a radical, producing stable byproducts including -carotene, ascorbic acid, uric acid, and -tocopherol (Halliwell 1996).

Protective effect of antioxidants on kidney damage: Increased ROS/RNS production is linked to oxidative stress-induced kidney injury. Furthermore, antioxidants effectively prevent oxidative stress-induced kidney damage (Rafieian-Kopaei 2013). Antioxidants

obtained from medicinal plants reduce kidney damage by lowering lipid peroxidation (LPO) and increasing endogenous antioxidants. Kidney damage is reduced by increased levels and activity of endogenous antioxidants. Supplementation with tocotrienol, a vitamin family member, reduced proximal tubular damage and renal LPO while also increasing GSH levels and catalase activity. It also has the ability to improve the $NO^{-}{}^{2}/NO^{-3}$generation index. Tocotrienol is a natural antioxidant that protects the kidneys from the damage caused by potassium dichromate (Rafieian-Kopaei 2013). Ligustrazine, an antioxidant alkaloid derived from Ligusticum wallichii, has been shown to protect kidneys from ischemia/reperfusion damage by increasing SOD activity, lowering ROS, and lowering MDA. Troxerutin, which is rich in cereal grains, tea, coffee, and a range of fruits and vegetables, has been proven to increase the activity of antioxidant enzymes such as Cu/Zn SOD, GPx, and catalase, as well as lower MDA levels. It has been proven in recent research to prevent oxidative stress-induced kidney damage (Rafieian-Kopaei 2013). Antioxidants, as previously stated, usually act by donating electrons to free radicals rather than becoming electron-scavenging compounds. It was discovered that persons who ate little vegetables and fruits had a higher chance of developing certain diseases than those who ate more. Although free radicals play a role in kidney damage. Diabetes, atherosclerosis, heart disease, nephrotoxicity, hepatotoxicity, cognitive impairment, and eyesight loss are all symptoms of diabetes. Despite the fact that many studies, particularly laboratory experiments, demonstrate that antioxidant supplements can help with various illnesses, extensive clinical trials do not always confirm that antioxidant supplements are effective. Have a significant impact on these illnesses Antioxidants, which are present naturally in vegetables, fruits, and grains, appear to help prevent a number of illnesses such as kidney injury. However, antioxidants do not work the same in all situations. The findings of extensive research show that ingesting single antioxidants like vitamin E or vitamin C protects against kidney injury and other oxidative stress-related disorders. While the findings of large trials provide little evidence that consuming single antioxidants protects against problems like kidney injury, the findings of combination studies are likewise convoluted and unclear (Rafieian-Kopaei 2013).

2.12 Enzymatic Antioxidants

Primary or constitutively functioning antioxidant enzymes (superoxide dismutase (SOD), catalase, glutathione (GSH) peroxidase, and thioredoxin) that function to maintain the reducing tone within cells and keep the redox balance steady, and (ii) antioxidant response element (ARE)-driven enzymes: phase 2 In times of inflammation or stress, genes code for enzymes that directly inactivate oxidants, boost GSH synthesis and regeneration, and stimulate NADPH synthesis. Upstream AREs, which are activated by the transcription factor nuclear factor erythroid 2-related factor 2, regulate them (Nrf_2). ARE-driven enzymes include Hume oxygenase-1 (HO^{-1}) and NADPH Quinone oxidoreductase (NQO^{-1}).

2.13 Antioxidant Therapy in Human Renal Injury

AKI is associated with a high rate of morbidity and mortality. Attempts to reduce the inciting drug/injury/illness, as well as renal replacement treatment (dialysis) to remove fluid overload and uremia, balance electrolytes, and rectify metabolic acidosis, are the mainstays of AKI prevention. It may be possible to avoid renal harm by addressing imbalances in nutrient-derived antioxidants, such as vitamin C, especially after severe injury and in critically ill and elderly patients who have depleted plasma antioxidants (Dennis and Witting 2017). Despite evidence of antioxidant efficacy in animal models of AKI and renal damage, the translation of antioxidant therapy to human studies has proven difficult. As a result, NC has been subjected to a number of studies, but the results have been mostly equivocal in terms of reducing CI- and other forms of AKI (Gojon and Morales 2020). Or renal illness (chronic). However, it has been shown to be beneficial in the treatment of end-stage renal illness and kidney transplantation. Vitamin E has contradictory effects, reducing or not reducing the incidence of chronic renal disease (Dennis and Witting 2017). Because of increased mortality (cardiovascular events) in the treatment arm, a clinical trial of the Nrf_2 pathway enhancer bardoxolone methyl on end stage renal disease among type 2 diabetes patients with chronic kidney disease was terminated (Impellizzeri *et al.* 2014).

2.14 Anti-Inflammatory and Antioxidant Compounds

Lifestyle variables such as aerobic exercise and nutritional changes can help CKD patients. (Ikizler *et al.* 2018) have been found to have anti-inflammatory effects; however, adherence is generally poor in CKD patients, prompting to the use of pharmaceutical therapy as a possible option. Statins are drugs that are used to lower cholesterol levels (Rapa *et al.* 2020) and AT1-blockers, as well as angiotensin-converting enzyme inhibitors, have been demonstrated to have anti-inflammatory effects (Su 2015). Even if some studies have suggested their indecency in dialysis patients (Lovell 1983). However, in addition to conventional therapy, the use of supplements has sparked scientific attention. Despite the fact that oxidative stress is involved, antioxidant treatments have not yet become a standard of care in CKD patients, and additional research is needed. Several studies have demonstrated that substances with anti-inflammatory and antioxidant properties can be used to treat CKD. Several groups of vitamins and minerals, as well as plant-derived metabolites, are becoming increasingly popular.

2.15 Antioxidant Agents in Kidney Disease

Inflammatory and oxidative stress markers have been linked to cardiovascular and renal outcomes in patients with CKD and ESRD in epidemiological investigations (Del Vecchio *et al.* 2011). Antioxidant medications appear to have positive benefits in animal models of renal illness, but outcomes in human research are limited and contentious. The treatment of tempol, an antioxidant SOD mimic, to hypertensive rats with early experimental diabetes mellitus restored the oxidative imbalance and reduced oxidative stress-induced kidney injury, lowering albuminuria and fibrosis (Weissman and Maack 2021). Antioxidant drugs tend to be beneficial in animal models of renal disease, but human study results are limited and controversial. Treatment of hypertensive rats with early experimental diabetes mellitus with tempol, an antioxidant SOD mimic, restored oxidative equilibrium and reduced oxidative stress-induced kidney injury, reducing albuminuria and fibrosis (Zhan *et al.* 2004). In conclusion, synthetic and natural antioxidants promoted renal and endothelial protection as well as a reduction in oxidative

stress in hypertensive rat models. Blocking the mitochondrial enzymes monoamine oxidases with pargyline 28 days after surgery decreased H_2O_2 production and enhanced renal function and renal inflammation (lower IL-1 and TNF- gene expression) in a model of ischaemia reperfusion and cyclosporine toxicity after unilateral nephrectomy (Chaaya *et al.* 2011). Apoptosis, necrosis, and fibrosis were all reduced when pargyline was given before ischemia reperfusion. Reduced expression of TGF-1, collagen types I, III, and IV, as well as stabilization of SOD1, catalase, and inflammatory gene expression, were linked to this impact. AST-120, an oral carbonic adsorbent, reduced oxidative stress in endothelial cells in models of renal chronic failure (5/6 nephrectomy rats), as evaluated by the oxidized/unoxidized albumin ratio. Reduced blood levels of indole sulfate, a uremic toxin that causes ROS, were used to achieve this result. The treatment of omega-3 fatty acids, a beneficial molecule in preventing atherosclerosis, greatly reduced various components of oxidative stress as well as indicators of inflammatory and fibrotic response in another model of residual kidney. In the remaining kidney, it also reduced tubulointerstitial fibrosis and inflammation. Treatment of anti-Thy1 glomerulonephritis with parthenolide, a triterpenoid anti-inflammatory drug, reduced renal inflammation via NF-kappa suppression, decreased MCP-1 and iNOS, and improved proteinuria, tubular, and glomerular damage (Chaaya *et al.* 2011).

Exogenous antioxidants have not been proved to have a positive effect in individuals with clinical hypertension, as they have been in animal models with hypertension or chronic renal failure (Rodrigo *et al.* 2011)

2.16 Potential Adverse Effects of Antioxidant Treatment

Excessive antioxidant treatment has been linked to a variety of side effects in several recent investigations (Namazi *et al.* 2016), including an increase in all-cause mortality (Ford *et al*. 2005), this is especially true when antioxidant supplements are used in ESRD patients. For example, some research suggests that high-dose vitamin C treatment may potentially enhance lipid peroxidation (De Mauri *et al.* 2020) or worsen clinical symptoms (Singer 2011), patients on hemodialysis, as a result, until well-designed large

clinical outcome trials are available, caution and proper monitoring should be suggested while using antioxidants in ESRD patients.

2.17 Antioxidant Enzymes

In several animal models of AKI, increasing antioxidant enzyme activity appears to be protective. SOD or catalase treatment reduces ROS in proximal tubule damage after hypoxia in vitro, according to early ischemia investigations (Dennis and Witting 2017). In rabbits with renal ischemia, SOD decreases oxygen radical's in vivo (Nilsson *et al.* 1993). SOD also enhanced renal function in rats, as well as reducing kidney tissue injury and cortical mitochondrial lipid peroxidation. In vitro and in vivo investigations confirmed that SOD decreased ROS and was cytoprotective to renal cells (reviewed in. Sepsis is reduced by pharmacologic drugs having SOD mimic action (Tempol, MnTMPyP). AKI caused by ischemia, as well as ischemia-induced AKI. MnTMPyP also reduces persistent increases in ROS and oxidative damage, as well as a decrease in SOD associated with kidney fibrosis following ischemic AKI (Kim *et al.* 2009). MnTMPyP inhibited the generation of O_2 and peroxynitrite in animal sepsis and corrected functional kidney deficits when given 6 hours after the septic insult, implying that antioxidant intervention is advantageous and that preventing ROS formation can alleviate microvascular failure and renal injury (Dennis and Witting 2017). In vitro, MnSOD overexpression, but not catalase, reduces cisplatin-induced kidney epithelial cell damage (Davis *et al.* 2001). Adding to the evidence that O_2 is vital in AKI. Hyperglycemia, which contributes to diabetic nephropathy, also generates O_2 within mitochondria and inactivates complex III, both of which can be mitigated by MnSOD overexpression (Hekimi *et al.* 2011).

MnSOD efficiently converts O_2 to H_2O_2, allowing ROS to exit the organelle. However, renal MnSOD inactivation (up to 50 percent) associated with increased mitochondrial O_2, has been demonstrated in mouse sepsis, and this can be attenuated with the mitochondria-targeted antioxidant Mito-TEMPO (Patil *et al.* 2014). Further, Mito-TEMPO mitigated renal mitochondrial and circulation dysfunction, together with doubling the survival rate,

and was effective when administered post-septic insult. Whether other low-molecular weight cyclic nitroxide SOD mimetics that also show anti-inflammatory activity independent of radical quenching. Can provide reno-protection, but more research is needed. In mice given cisplatin, Mito-CP, a SOD mimic, also targets mitochondria and protects against tubular cell dysfunction, damage, apoptosis, and inflammation, as well as reduced $NOX_{2/4}$ mRNA (Dennis and Witting 2017).

2.18 Antioxidant Therapy in Human Renal Injury

Despite evidence of antioxidant efficacy in animal models of AKI and renal damage, translating antioxidant therapy to human research has been difficult. As a result, various trials of Nac have been conducted, however the results have been mostly equivocal in terms of reducing CI- and other AKI symptoms (Dennis and Witting 2017). Or chronic kidney disease. However, it has been shown to be beneficial in the treatment of end-stage renal illness and kidney transplantation. Vitamin E has contradictory effects, reducing or not reducing the incidence of chronic renal disease. Because of increased mortality (cardiovascular events) in the treatment arm, a clinical trial of the Nrf_2 pathway enhancer bardoxolone methyl on end stage renal disease among type 2 diabetes patients with chronic kidney disease was terminated (Dennis and Witting 2017).

2.19 Hyperuricemia and Chronic Kidney Disease

The end result of purine metabolism in humans is UA. Xanthine oxidase catalyzes the final oxidation of hypoxanthine and xanthine to UA in this route. Unlike humans, most other mammals have an additional purine metabolic enzyme called urease (Urate oxidase) (Glantzounis *et al.* 2005). Uri case converts UA to 5-hydroxyisourate and allantois, a very water-soluble molecule that is eliminated most effectively in urine. Primates lost urease function and the ability to manufacture allantois enzymatically early in evolution due to different gene mutations. As a result, humans have far greater serum UA levels than other mammals, and hyperuricemia can develop quickly. UA is a weakly soluble weak organic acid that circulates in the blood as the urate anion at a physiological pH of 7.40 (Prakash

2014). Hyperuricemia can be caused by an increase in UA production or a decrease in UA secretion. Hyperuricemia has no commonly accepted definition. Physio chemically, it is characterized as a serum urate concentration greater than its solubility point (6.8 mg/d.). Monosodium urate crystals grow at amounts above their solubility and precipitate in joint tissues, causing gout (Schorn *et al.* 2012**)**.

The kidneys are responsible for the majority of daily UA excretion (65 – 75%), with the gastrointestinal system excreting the remaining (25 – 35%). The glomerulus filters urea readily, but due to net proximal tubular reabsorption, its fractional excretion is only 10%. The tubular management of UA is still a work in progress, although it has recently been discovered that it includes reabsorption and secretion in the proximal tubule. Hyperuricemia is caused by poor renal excretion in around 90% of cases, according to research (Schorn *et al.* 2012**)**. In the advanced stages of (CRF) prevalence of hyperuricemia exceeds 60%. Also, CRF is one of the most common independent risk factors for gout (Sah and Qing 2015). There is no doubt that hyperuricemia and CRF have a significant association, although the specifics of that relationship are still up for debate. The apparent causal link between hyperuricemia and CRF, in particular, is a matter of debate. Hyperuricemia has been recognized as a risk factor for developing or progressing CRF in the previous two decades.

Treatment of patients of CRF with high uric acid: The link between hyperuricemia and (CRF) was once thought to be due to a reduction in uric acid elimination. Uric acid was once thought to be a marker for renal impairment, however recent observational studies have suggested that uric acid may have a role in the development of CRF. The strongest evidence for the function of uric acid in the development of cerebral vascular disease and renal injury came from animal research. Induction of afferent arteriolopathy, inflammation, and stimulation of the renin-angiotensin system are some of the postulated mechanisms of uric acid-induced kidney injury (Bonino *et al.* 2020). In a study conducted by Sanchez-Load, rats given ovonic acid had a two-fold increase in uric acid levels, which was related with a 10-mm Hg rise in systolic blood pressure and an 18-mm Hg rise in mean arterial blood pressure. The authors concluded that hyperuricemia induces arteriolopathy of the preglomerular blood vessels, which inhibits the autoregulatory

response of the afferent arterioles, culminating in glomerular hypertension, based on histologic findings. The authors also suggest that arteriolar thickening causes renal hypoperfusion, which enhances the production of nitric oxide. tubulointerstitial inflammation and fibrosis (Murakami and Sozio 2013). The fact that when ovonic acid was given with allopurinol, both the rise in blood pressure and the afferent arteriolar thickening were avoided further substantiated the link between hyperuricemia, hypertension, and arteriolar thickening (Sanchez-Lozada *et al.* 2005). Unlike animal research, human cross-sectional studies yield less simple outcomes. A Japanese study of 6403 people with normal renal function who lived in Okinawa City found that, aside from gender, serum uric acid is the most significant predictor of developing high serum creatinine during a two-year period. This study also found that a serum uric acid level of less than 8.0 mg/dL is linked to a 2.9-fold risk of high serum creatinine in men and a 10-fold risk in women. The Cockcroft-Gault equation did not indicate a correlation between baseline uric acid levels and the change in creatinine clearance, and the Cockcroft-Gault equation did not show a correlation between baseline uric acid levels and the change in creatinine clearance. Authors did not explain this. The same investigators also identified uric acid in women as an independent predictor of renal failure requiring renal replacement therapy during a 7-year follow-up period, but the results in men failed to reach statistical significance (Domrongkitchaiporn *et al.* 2005).

2.20 Anemia of Chronic Renal Disease

Chronic Kidney Disease (CKD) anemia is a type of cellular, chromosomal, and hypoproliferative anemia caused by chronic kidney disease. It is frequently linked to poor outcomes in chronic renal disease and increases mortality risk. The goal of treatment is to improve kidney function and, if possible, increase red blood cell production. Anemia caused by chronic renal disease is best treated with Erythrocytosis and iron supplementation. This activity examines the diagnosis and treatment of anemia in patients with chronic renal disease. Hemoglobin levels of less than 13.0 g/ld. in men and less than 12.0 g/d. in premenopausal women are considered anemia (Fang and He 2020). Chronic kidney disease (CKD) anemia is a type of hypoproliferative, normocytic, normochromic anemia. It is frequently related with poor CKD outcomes and increases mortality, among

other CKD problems (Khoury *et al.* 2021). When the glomerular filtration rate falls below 60 mg/ml, the disease begins to manifest. When the GFR is greater than 80 mg/mL, anemia is uncommon. The anemia becomes more severe as the GFR declines. Due to reduced dietary iron absorption, persistent bleeding due to platelet dysfunction from uremia, frequent phlebotomy, and blood trapping in the dialysis system, patients with CKD are at an elevated risk of iron shortage. This shortage, together with the depletion of the circulating iron pool caused by ESA stimulation of erythropoiesis, makes iron supplementation the cornerstone of CKD anemia management. In hemodialysis patients, intravenous iron is preferred due to lower oral iron absorption (Babitt and Lin 2012).

2.21 Blood Calcium

Calcium is one of the chemical elements required for the body's cells to operate properly. In particular, the brain muscles and heart require a healthy quantity of calcium in the blood. Calcium enters the body through food and is absorbed into the body through the digestive system, where a portion of the calcium in the blood enters the cells (Vrij *et al.* 2015).

2.22 Calcium Balance in Chronic Kidney Disease

Calcium balance is defined as whole-body calcium retention or deficit, which is computed by subtracting entire body calcium losses from total calcium intakes. The physiological processes that govern calcium balance, however, make it more complicated, especially in CKD Furthermore, conducting calcium balance research is time-consuming and fraught with difficulties (Gallant and Spiegel 2017). Important factors to consider and challenges to overcome when creating and implementing these research. There are further issues that are peculiar to the CKD group. The primary principle of calcium balance studies is that the research participants must be in a steady state, which means that there must be no significant changes in inputs or outputs over the course of the balancing period. This involves the adoption of a well-controlled and consistent dietary intake that begins at least one week before the balance measurements are taken (Gallant and Spiegel 2017). The

fecal calcium: PEG excretion ratio can be determined and used to identify when people have equilibrated to a new regulated dietary calcium intake level using the non-absorbable fecal marker polyethylene glycol (PEG) (i.e., when the fecal calcum: PEG ratio stabilizes). This has been found to happen after 6 days in adults, which is why a 1-week run-in on a regulated diet is recommended before beginning balance measures (Gallant and Spiegel 2017). The requirement for steady state prevents formal balance investigations in dialysis patients since dialysis affects calcium balance and may induce fluxes in soft tissue and bone mineral content, making true steady state impossible to accomplish. The second key assumption of calcium balance studies is that food intake must be well regulated and all inputs and outputs must be precisely measured. Diets should be managed in calcium balance studies to ensure regular levels of calcium, as well as other nutrients known to affect calcium balance, such as phosphorus, salt, and magnesium. Nutrient databases are a good place to start when creating a controlled diet, but they're not without flaws, therefore pre-study composite meals must be chemically evaluated for nutrient content and adjustments made to meet target values. The expertise of registered dietitians who specialize in research diet design is often required for sophisticated diet design for balancing studies. Duplicate meals should ideally be created alongside the meals provided to subjects during balance experiments, and these duplicate meals should be evaluated to offer the most precise measurement of actual food consumption feasible. Furthermore, individuals must be expected to consume exclusively and completely (Lasisi *et al.* 2016).

2.23 Creatinine

The most widely available and widely utilized biomarker of renal function is creatinine. It is derived from creativity, which is a fast-acting energy reserve in muscles. Creatinine is formed by the spontaneous and irreversible conversion of creative to its anhydride form. While creatinine is filtered readily and reabsorbed in small amounts, the proximal tubule secretes 20 – 30% of it. As a result, the Jaffe method overestimates the creatinine while underestimating the eGFI, however this is partially countered by the non-creatinine chromogens. A further limitation of using creatinine to determine GFR is evidenced by the curvilinear relationship between creatinine and GFR, which makes it prone to not

being able to detect mild to moderate reductions in GFR clearly (1)—if the reference interval of creatinine is 50–100 mol/L, and a patient has an initial result of 50 molls/L and folic oocytes per million (of this stresses two crucial things about creatinine: eGFI should be utilized to track renal function whenever possible. Comparing a patient's values to their past values is more essential than comparing a patient's values to a reference interval (See formula section), and comparing a patient's values to their previous values is more significant than comparing a patient's values to a reference interval. The Jaffe reaction and its modifications are the most extensively used methods for determining creatinine levels (Manuwar *et al.* 2020). When creatinine reacts with alkaline picrate, a color change is detected. It is susceptible to a number of common interferons, including ketones (positive interfering) and bilirubin, despite being relatively inexpensive and extensively used (negative interfering) (Gubala *et al.* 2012). Various enzymatic techniques and chromatographic methods are also utilized to determine creatinine levels. Enzymatic methods, which are commonly employed in point-of-care testing, are typically more expensive than the Jaffe method, although being less related with interferons (but not immune). They frequently utilize hydrogen peroxide in their processes, therefore they could be harmed by an antioxidant like vitamin C (Thérond *et al.* 2000).

2.24 Urinary Biomarkers of Kidney Disease

Because the first signs of kidney impairment occur in the tubular cells, and then the urine in the lumen, urinary biomarkers may have an advantage over blood biomarkers (Bagshaw *et al.* 2007). As a result, they are more sensitive to changes in renal function, with aberrant results often appearing during the first day of renal impairment.

2.25 Urea

Proteins turn over at varied rates throughout the body: examine the short half-lives of transcription factors compared to the prolonged half-lives of muscle structural proteins. Biochemical processes that correctly identify proteins to be degraded, as well as systems that efficiently breakdown doomed proteins, are required to produce such distinctions. As

a result, these mechanisms do not interfere with protein turnover, which is essential to maintain cellular functions. The “how” and “why” of the biochemical reactions that are required for maintenance of cellular functions are being uncovered (Weiner *et al.* 2015). We'll look at urea's overall metabolism and activities in this section. Because urea is the most common circulating source of nitrogen-containing molecules and plays a key role in kidney function, understanding its activities and metabolism is crucial. Protein-rich foods are broken down into 9 essential and 11 non-essential amino acids (See Figure 2.1). Urea generation is inversely proportional to the quantity of protein consumed, hence urea can be used to determine whether a patient with CKD is getting the proper amount of protein (Piccoli *et al.* 2020). Furthermore, urea production is used to assess the buildup of putative uremic toxins and, as a result, as a guideline for managing CKD patients' diets.

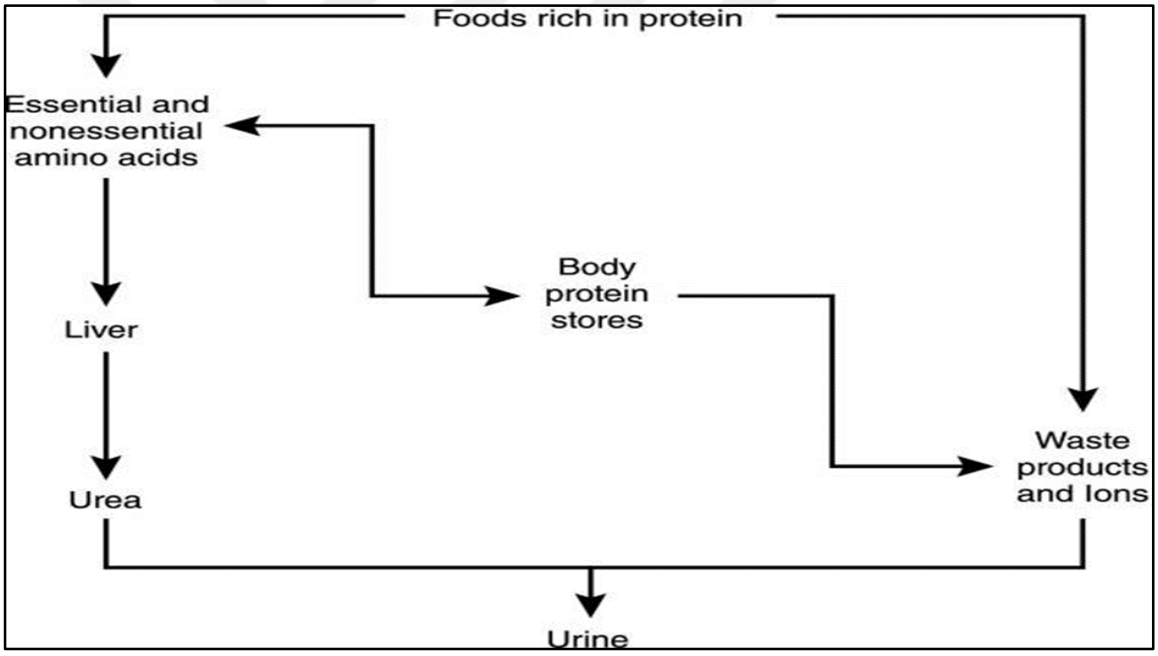

Figure 2.1 Overview of protein metabolism (Piccoli *et al.* 2020)

2.26 Albumin

Albumin (molecular weight 65 kDa) filtered in the glomeruli is thought to be a primary source of urine albumin. Tubular reabsorption occurs in tandem with albumin filtration.

2.27 Urinary Albumin and Protein

Urinary albumin and protein have the ability to both suggest and cause renal disease. The question of whether to test albumin or protein levels in urine is still up for debate (Piccoli *et al.* 2020). The existence of tubular or overflow proteinuria may be missed if just albumin is tested, however albumin has been reported to correspond more closely with kidney disease progression in diabetes and glomerular disease in hypertension. Choosing which to utilize is frequently dictated by the clinical situation. In diabetes mellitus, albumin should be utilized to check for microalbuminuria, whereas proteinuria is indicated in preeclampsia testing. (Bökenkamp 2020).

Urinary albumin levels are considered clinically superior to total protein levels unless a specified total protein level is required. Albuminuria can be caused by a variety of factors other than renal illness, including upright posture, heart failure, and urinary tract infection. As a result, spot urines should be taken when you first wake up, and the urinary albumin: creatinine ratio should be calculated. It's important to remember that there are gender-specific cut-offs, and positive results should be confirmed, with two out of every three positive results within a month indicating albuminuria. Urinary albumin is commonly measured in the laboratory using a sensitive immunize photometric method, turbid metric, though dipstick, electrophoresis, and liquid chromatography are also used. Chromatography does exist (Mikolasevic *et al.* 2017).

Differences arise within and between procedures, in part because different tests detect distinct fragments and alterations of albumin in different ways (Betzel *et al.* 2020). Protein is potentially analyzed using a number of methods, including colorimetric, electrophoretic, or cephalometric assays (Treacy *et al.* 2019). There are discrepancies in results between several methods, including related dye-binding tests such as Coomassie Brilliant Blue and Pyrogallol Redmolybdate, underscoring the necessity for a common calibrator, or standardization program, between methodologies (Proteins fewer than 5 kDa are usually filtered fully, proteins larger than this but smaller than albumin (66 kDa) are usually partially filtered, and proteins larger than albumin are usually kept. Small

proteins such as A1M, is mostly filtered at the glomerulus, but 99% is reabsorbed by the proximal tubule cells in health Zhang (Fang and He 2020). The A1M: creatinine ratio in urine will rise if tubular performance is impaired. Albumin is generally prevented from entering the glomerular, despite the fact that it is typically 99 percent reabsorbed by the proximal tubule cells in health (Travis *et al.* 2015).

3. MATERIALS AND METHODS

3.1 Materials

3.1.1 Equipment

The real photos of the laboratory medical equipment's that used in the present study are illustrated in Appendices.

3.1.2 Chemicals

- HRP –Conjugate Reagent.
- Sample Diluent.
- Chromogen Solution A.
- Chromogen Solution B.
- Stop Solution.
- Wash Solution.

3.1.3 Preparation of blood samples

3CCS of blood samples were obtained from patients with renal failure with uninfected patients, the blood sample was left for 20 minutes at room temperature after coagulation and the blood was separated by centrifugation at 2000xg for 10 minutes.

3.2 Experimental Method

This ELISA Kit uses sandwich-ELISA as the method. The micro Elisa strip plate provided in this Kit has been pre-coated with an antibody specific to CoQ10. Standards or samples are added to the appropriate micro Elisa strip plate wells and combined to the specific antibody. Then a Horseradish CoQ10 (HRP) conjugated antibody specific for

CoQ10 is added to each Micro Elisa strip plate well and incubated (See Table 3.1). Free components are washed away. The TMB substrate solution is added to each well. Only those wells that contain CoQ10 and HRP conjugated CoQ10 antibody will appear blue color and then turn yellow after the addition of the stop solution the optical density (OD) is measured spectrophotometric ally at a wavelength of 450 nm. The OD value is proportional to the concentration of CoQ10. You can calculate the concentration of CoQ10 in the samples by comparing the OD of the samples to the standard curve.

Table 3.1 Materials supplied in human Coenzyme Q10 (CoQ10) Elisa kit

Coenzyme Q10(CoQ10) Elisa kit	**The Amount of Pıpette**
HRP-Conjugate reagent	6mL x 1 bottle
Sample diluent	6mL x 1 bottle
Chromogen A solution	6ml x 1 bottle
Chromogen B solution	6mL x 1 bottle
Stop solution	6mL x 1 bottle
Wash solution	20mL – 30mL x 1bottle

Assay procedure

1. Dilution of standards by small tube first. Then pipette the volume of 50uL from each tube to microplate well. Each tube uses two wells. Total ten wells.
2. In the micro Elisa strip plate leave a well empty as blank control in sample wells. 40uL sample dilution buffer and 10ul sample are added (dilution factor is 5) samples should be loaded onto the bottom without touching the well wall. Mix well with gentle shaking.
3. Incubation: incubate 30 min at 37^{o}C after sealed with closure plate membrane.
4. Dilution: dilute the concentrated washing buffer with distilled water (30 times for 96T and 20 times for 48t).
5. Washing: carefully peel off closure plate membrane. Aspirate and refill with the wash solution. Discard the wash solution after resting for 30 second. Repeat the washing procedure for 5 times.

6. Add 50 µL HRP-Conjugate reagent teach well except the blank control well.
7. Incubation as described in step 3.
8. Washing as described in step 5.
9. Coloring Add 50µL chromogen solution and 50µL chromogen solution B to each well. Max with gently shaking and incubate at 37^0C for 15 minutes. Please avoid light during coloring.
10. Termination add 59µL stop solution to each to terminate the reaction. The color in the well should from blue to yellow.
11. Read absorbance O.D at 450nm using a microliter plate Reader. The OD value of the blank control well is set zero. Assay should be carried out within 15 minutes after adding stop solution.

3.2.1 Total antioxidants Capacity assay the CUPRAC Method

Principle

Total antioxidants + Cu^{+2} _____ Cu^{+}

Cu^{+2} +2.9-dimethyl-1, 10 -phenanthroline _____complex (ƛ max at 450 nm)

Reagents

1- Copper (11) chloride solution at a concentration of 10^{-2}M in DW
2- Ammonium acetate buffer(1M) pH=7.0 in DW
3- Neocuproine (NC) {2.9-dimethyl-1,10-phenanthroline were} solution at a concentration of 7.5 x 10^{-3}M IN ethanol.
4- Th standard solution of sample antioxidants were prepared at 1.0 x10^{-3}M concentration α-tocopherol was dissolved in dichloromethane (DCM). Ascorbic acid and glutathione (GSH) SOLUTION WERE prepared in distilled water.
5- Working standard solution: composed of three equal volume of 1.0 x 10^{-3}M ascorbic acid and 1.0 x10^{-3}M glutathione (GSH).

The Reagents procedure that used in the present study are illustrated in Table 3.2.

Table 3.2 Reagents and other details

Reagents	Test	STD	
Copper(H)chloride solution	1mL	1 mL	1 mL
Sample	50µL	--	--
Working standard solution	--	50µL	--
DW	--	--	50µl
Neoeuproine (Ne) solution	1 mL	1 mL	1 mL
Ammonium acetate Buffer	1 mL	1 mL	1 mL

Test tube was mixed by vortex and incubated for 30 minutes at 37^{o}C, after that the absorbance was read on spectrophotometer at 450 nm.

3.2.2 Theoretical foundations

Subjects and study design: The study was conducted on both men and women (30-80) with renal failure and healthy ones in Kirkuk General Hospital in 4 groups as follows:

1- Group 19 women with Chronic Renal Failure.
2- Group 33 were men with chronic renal failure.
3- Group of 11 women did not have chronic renal failure.
4- A group of 11 men who did not have chronic renal failure.

4. RESULTS AND DISCUSSION

This study included a group of 82 blood samples, 72 patients with kidney failure and 30 healthy samples, aged between (30 - 80) years, and the results were as follows:

4.1 Urea, Creatinine, Albumin, Cholesterol Concentration of the Patients and Controls

The results in Table 4.1 and Figure 4.1 showed a significant ($P \leq 0.0001$) increase in the concentrations of creatinine (1.01 ± 0.24 b, 6.57 ± 2.32) and urea (149.40 ± 39.53, 30.26 ± 9.02 b) in The group infected with CRF respectively, while the same concentration or slight change in cholesterol albumin in the same group. Chronic Kidney Disease (CKD) is a progressive reduction in renal function (Dhanasekaran *et al.* 2014). Serum urea and creatinine are most widely accepted parameters to assess Chronic Kidney Disease (CKD) status as well as to assess renal status in susceptible diabetic and hypertensive subjects. There are no significant differences in the levels of albumin are observed in patient when compared to healthy control as well there is no significant differences in the levels of cholesterol are observed in patient when compared to healthy control.

Table 4.1 Urea, creatinine, albumin, cholesterol concentration of the patients and controls

Groups	Mean (mg/dL) ± SD				N
	Urea Test	Creatinine	Albumin	Cholesterol	
Control	30.26b ± 9.02	1.01b ± 0.24	3.90a ± 0.40	184.20a ± 31.76	30
Patients	149.40a ± 9.53	6.57a ± 2.32	3.99a ± 0.40	198.61a ± 36.81	52
P value	0.0001	0.0001	0.088	0.114	82

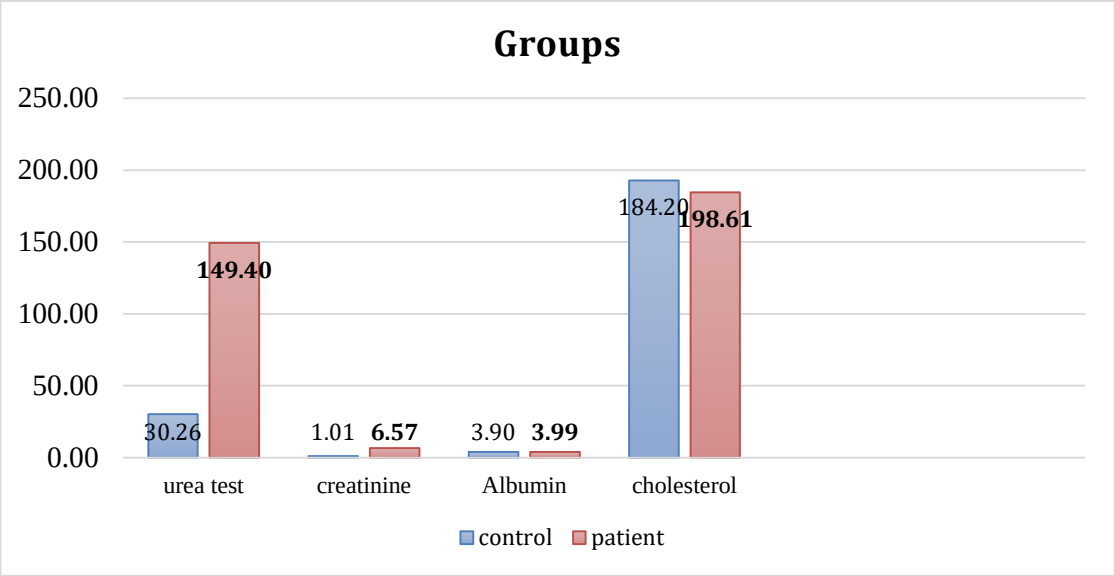

Figure 4.1 The level of urea, creatinine, albumin, cholesterol concentration of the patients group and control group

The results shown in the Table 4.2 and Figure 4.2 that there was a significant increase ($P \leq 0.0001$) in the concentration of the antioxidant, and coanzQ10 in patients with CRF respectively compared with the control group which is (1.23b ± 0.13), (1.60a ±0.27), and coq10 $P \leq 0.0004$, (0.88 ±0.69b), (1.60 ±79): Therefore, we found an apparent difference between them and through the values of ($P \leq 0.0001$), ($P \leq 0.0004$).

Table 4.2 The concentration of antioxidant and coanzQ10 of control group and patient group

Groups	**Mean (µL) ± SD**		**N**
	Antioxidant	**Coanzq10**	
Control	1.23b ± 0.13	0.88b ± 0.69	30
Patients	1.60a ± 0.27	1.60a ± 0.79	52
P value	0.0001	0.0004	82

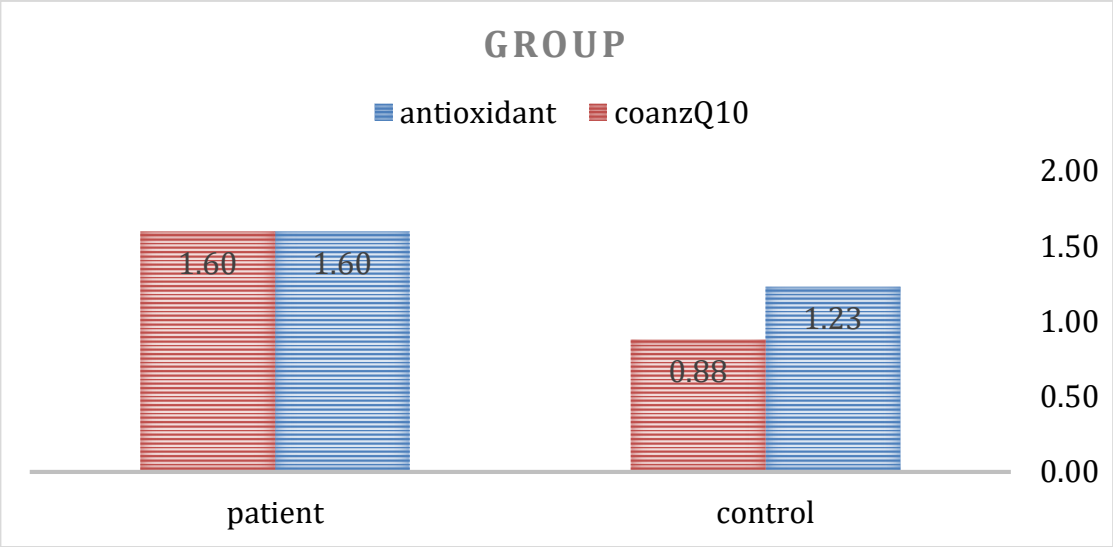

Figure 4.2 The level of antioxidant, coanzQ10 of the patient group and control group

The results in Table 4.3 and Figure 4.3 showed that there was no significant difference in the concentration of creatinine (4.39a ± 3.19, 4.78a ±3.42), urea (3.97a ± 0.41, 111.57 a ±71.08), albumin (3.97a ± 0.41, 3.94a ± 0.39), and cholesterol (193.07a ± 28.81, 178.16a ± 42.77) between males and females in CRF, respectively, compared to the control group, in the results shown in the Table 4.3.

Table 4.3 Comparison of gender between males and females in all studied groups for urea, creatinine, albumin, and cholesterol

Gender	**Mean (mg/dL) ± SD**				**N**
	Urea Test	**Creatinine**	**Albumin**	**Cholesterol**	
Male	102.5a ± 63.24	4.39a ± 3.19	3.97a ± 0.41	193.07a ± 28.81	52
Female	111.57a ± 71.08	4.78a ± 3.42	3.94a ± 0.39	178.16a ± 42.77	30
P value	0.551	0.609	0.773	0.063	82

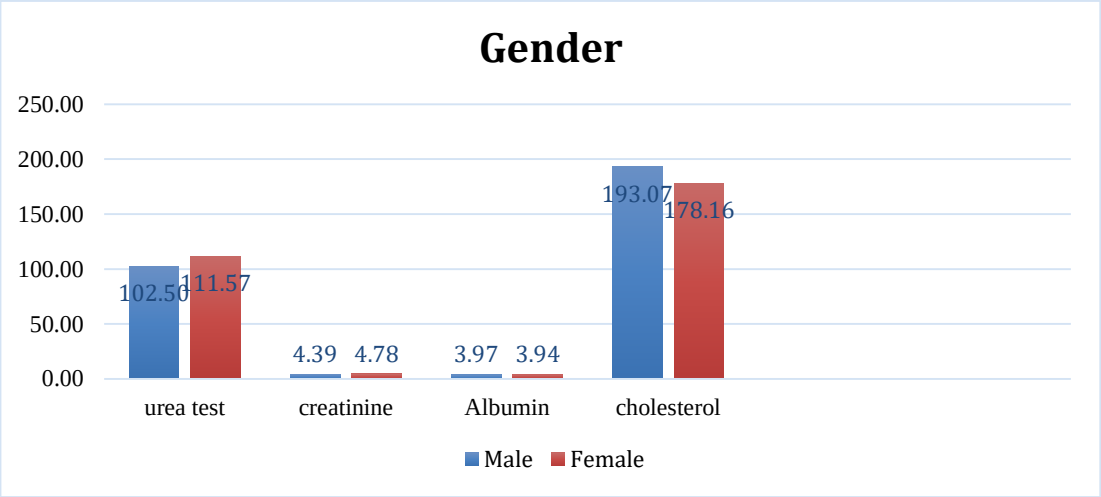

Figure 4.3 Comparison of Gender between males and females in all studied groups groups for urea, creatinine, albumin, and cholesterol

The results in Table 4.4 and Figure 4.4 showed that there was no significant difference P≤0.152 in coenzyme q10 and total antioxidant concentration P ≤ 0.361 between males and females (1.44a ± 0.26, 1.50a ± 0.33, 1.23a ± 0.79, 1.51a ± 0.87) in CRF respectively compared to the control group.

Table 4.4 Comparison by Gender between males and females in all studied groups for total antioxidant and coanzQ10

Gender	Mean (µL)	± SD	N
	Total antioxidant	CoanzQ10	
Male	1.44a ± 0.26	1.23a ± 0.79	52
Female	1.50a ± 0.33	1.51a ± 0.87	30
P value	0.361	0.152	82

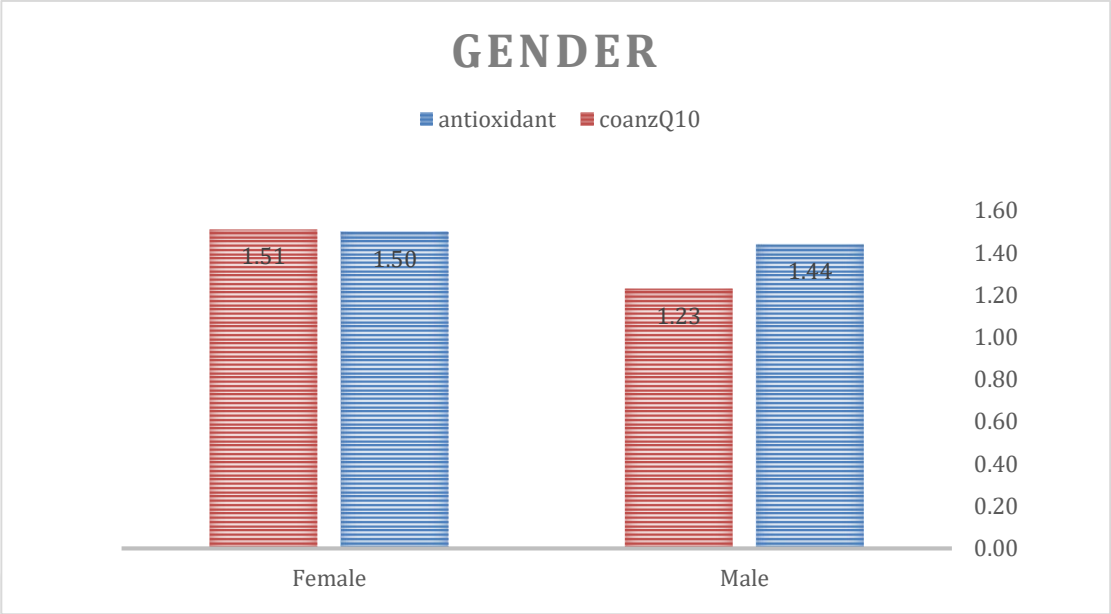

Figure 4.4 Comparison by Gender between males and females in all studied groups for total antioxidant and coanzQ10

The results show in Table 4.5 and Figure 4.5 between the age groups that there was no significant difference (P ≤ 0.538) in the concentration of urea and creatinine (P ≤ 0.680) in the following test, while there was a significant difference (P ≤0.006) in albumin and no significant difference (P ≤ 0.513) in cholesterol compared to the control group.

Table 4.5 Age Comparison between all groups for urea, creatinine, albumin, and cholesterol

Age	Mean (mg/dL) ± SD				N
	Urea Test	Creatinine	Albumin	Cholesterol	
30≥	110.67a ± 83.38	3.88a ± 3.39	3.2ab ± 0.42	181.22a ± 43.25	18
40≥	122.72a ± 57.52	3.98a ± 3.02	3.91bc ± 0.32	187.22a ± 30.87	18
50≥	153.83a ± 66.80	4.88a ± 3.66	4.17a ± 0.48	195.28a ± 40.21	18
60≥	167.57a ± 56.05	4.91a ± 3.20	4.92abc ± 0.30	198.29a ± 35.43	14
	171.07a ± 61.81	4.96a ± 3.09	4.98c ± 0.29	201.14a ± 21.17	14
P value	0.538	0.680	0.006	0.513	82

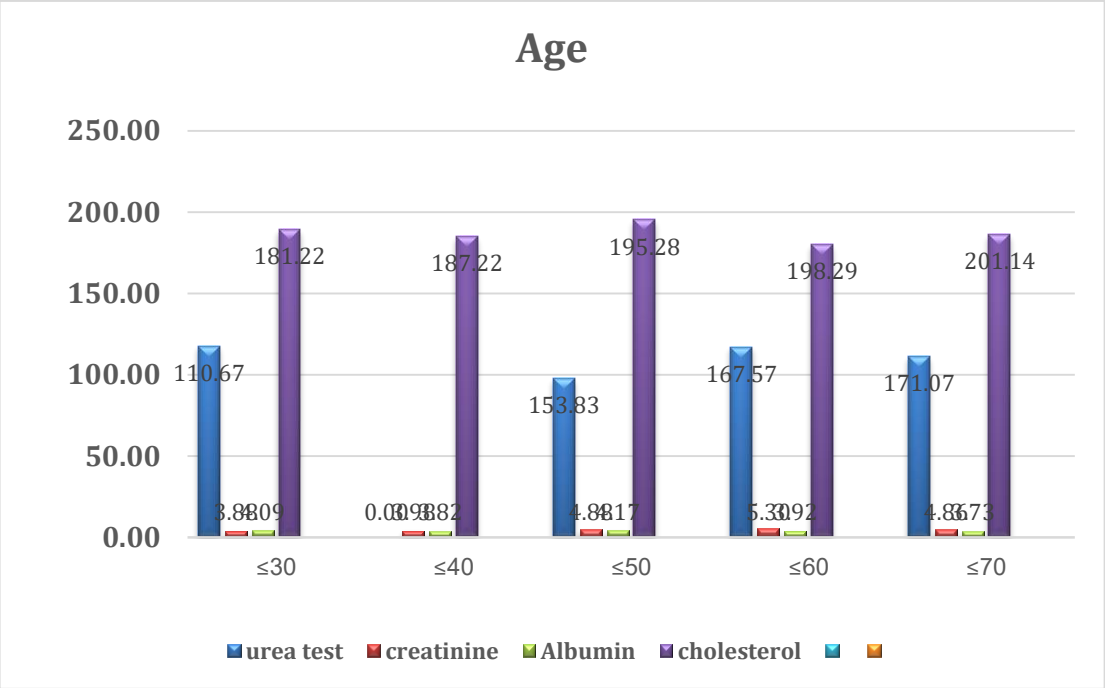

Figure 4.5 Age comparison between all groups for urea, creatinine, albumin, and cholesterol

The results in Table 4.6 and Figure 4.6 showed that there was no significant difference P ≤ 0.813 in total antioxidant concentration, while significant difference was found in CoanzimQ10, P ≤ 0.040 in CRF, respectively, between age groups compared to the control group, we observed a low level of Coanzimq10 and antioxdint in the age group of (70 – 80).

Table 4.6 Age comparison between all groups for total antioxidant and coanzQ10

Age	Mean (µL)	± SD	N
	Total antioxidant	CoanzQ10	
30≥	1.44a ± 0.29	1.73b ± 0.78	18
40≥	1.50a ± 0.34	1.70ab ± 0.84	18
50≥	1.47a ± 0.27	1.62a ± 0.91	18
60≥	1.45a ± 0.29	1.35ab ± 0.87	14
70≥	1.12a ± 0.23	0.96b ± 0.43	14
P value	0.813	0.040	82

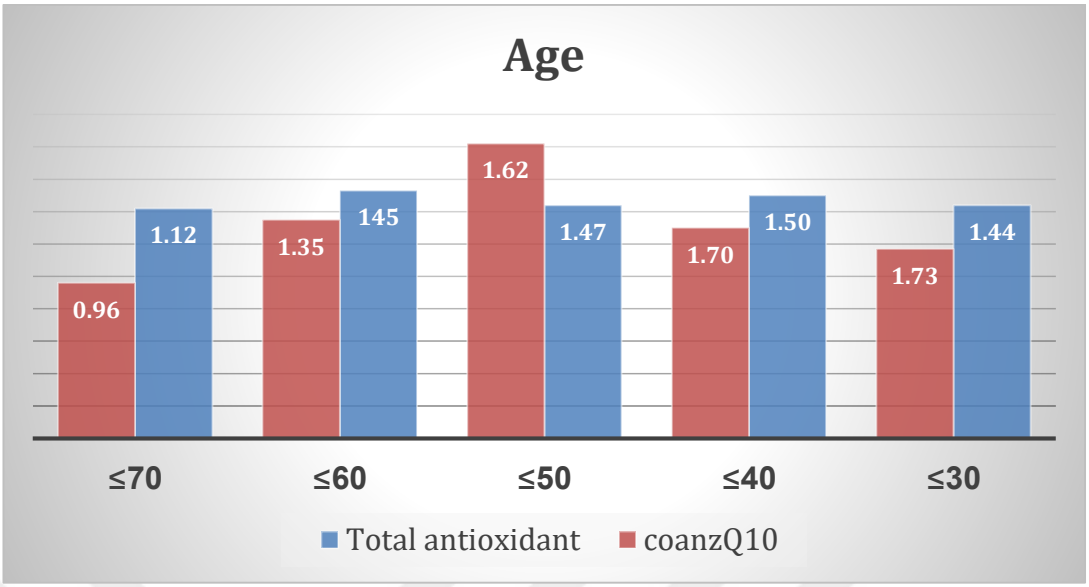

Figure 4.6 Age comparison between all groups for total antioxidant and coanzQ10

The results in Table 4.7 and Figure 4.7 showed a significant difference ($p \leq 0.0001$) between all age groups in patients and healthy subjects in the concentration of urea, creatinine ($p \leq 0.0001$), and albumin $p \leq 0.035$ And there was no significant difference in $p \leq 0.851$ cholesterol compared to the control group.

Table 4.7 Comparison age and groups by in all studied groups for urea, creatinine, albumin, and cholesterol

Age	Groups	Mean (mg/dL) ± SD				N
		Urea test	Creatinine	Albumin	Cholesterol	
30≥	Control	31.38c ± 10.75	1.03b ± 0.23	4.09ab ± 0.42	176.50a ± 33.83	8
	Patient	120.70a ± 33.60	2.17a ± 2.95	5.10ab ± 0.45	185.20 ± 47.11	10
40≥	Control	32.86c ± 10.07	1.00b ± 0.26	3.82abc ± 0.38	180.43a ± 23.47	7
	Patient	124.91b ± 43.12	3.88a ± 2.30	5.51abc ± 0.30	183.18a ± 35.75	11
50≥	Control	31.88c ± 9.24	0.99b ± 0.25	4.04ab ± 0.42	194.63a ± 34.07	8
	Patient	150.60b ± 37.46	3.90a ± 1.05	5.67a ± 0.51	195.80a ± 46.38	10
60≥	Control	36.00c ± 4.35	0.86b ± 0.23	3.69bc ± 0.15	181.33a ± 57.11	3
	Patient	157.55b ± 29.64	4.52a ± 2.41	5.79abc ± 0.30	186.00a ± 31.30	11
70≥	Control	37.25c ± 5.90	1.14b ± 0.31	3.56c ± 0.29	180.00a ± 16.26	4
	Patient	161.40b ± 30.41	5.35a ± 2.29	5.8bc ± 0.28	188.60a ± 23.15	10
P value		0.0001	0.0001	0.035	0.851	82

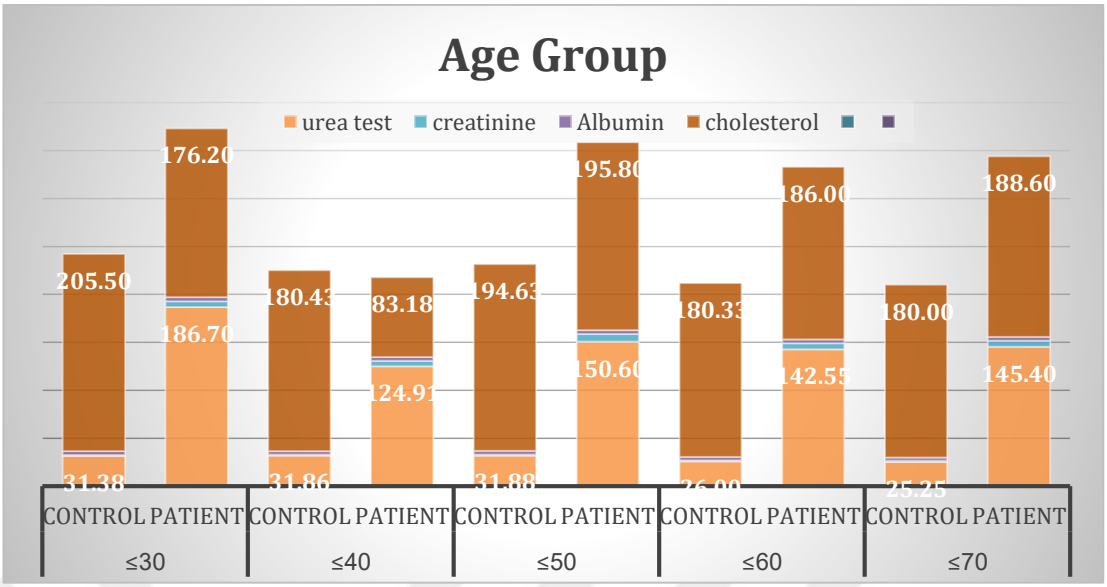

Figure 4.7 Comparison age and groups in all studied groups for urea, creatinine, albumin, and cholesterol

The results in Table 4.8 and Figure 4.8 showed a significant difference $P \leq 0.0001$ in the concentration of total antioxidants and a significant difference in CoanzimQ10, $P \leq 0.0001$, respectively, between the age groups of the control group and patients and a decrease in the age group (70 - 80).

Table 4.8 Comparison age and groups control will patient in all studied groups for total antioxidant and coanzQ10

Age	Groups	Mean (µL) ± SD		N
		Total antioxidant	CoanzQ10	
30≥	Control	1.22c ± 0.12	1.00bcd ± 0.69	8
	Patient	1.61a ± 0.27	1.30bc ± 0.85	10
40≥	Control	1.24bc ± 0.16	0.72cd ± 0.44	7
	Patient	1.68a ± 0.33	1.66ab ± 0.84	11
50≥	Control	1.25bc ± 0.16	1.27bc ± 0.95	8
	Patient	1.60a ± 0.24	2.25a ± 0.61	10
60≥	Control	1.29bc ± 0.15	0.39d ± 0.18	3
	Patient	1.60a ± 0.29	1.61ab ± 0.80	11
70≥	Control	1.21c ± 0.11	1.49cd ± 0.17	4
	Patient	0.59ab ± 0.22	0.34bcd ± 0.35	10
P value		0.0001	0.0001	82

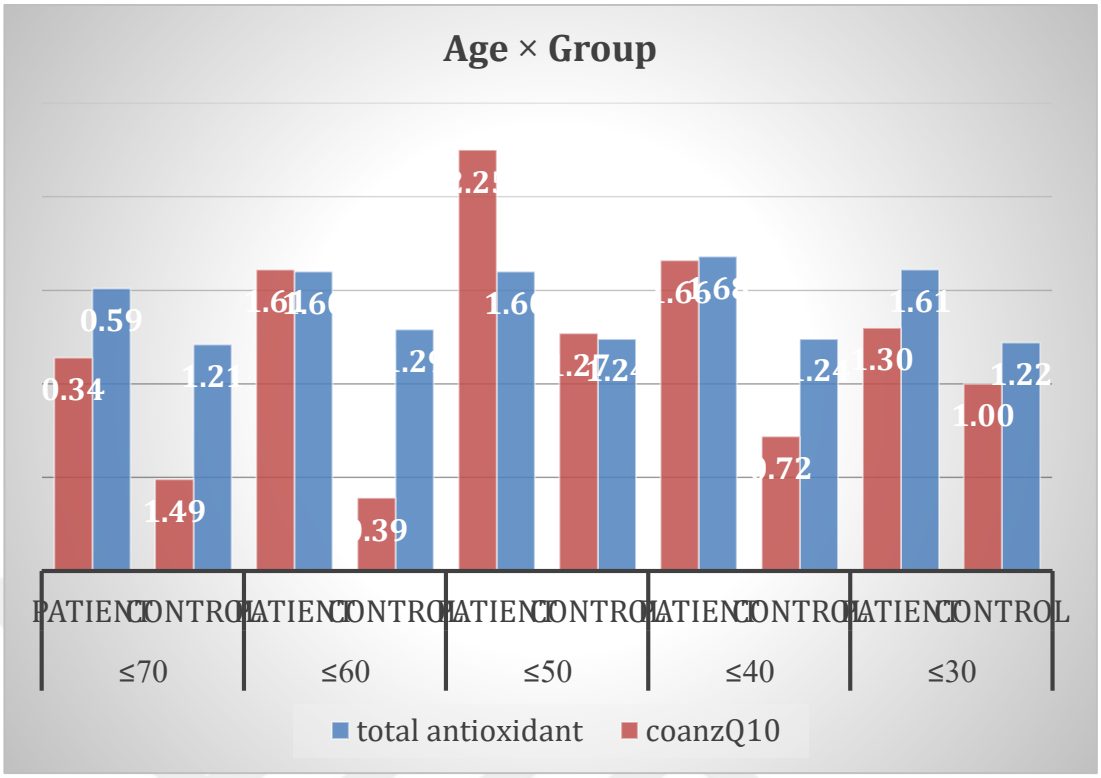

Figure 4.8 Comparison age and groups in all studied groups for total antioxidant and coanzQ10

The results in Table 4.9 and Figure 4.9 showed a significant difference ($P \leq 0.0001$) between males and females in the urea and creatinine $P \leq 0.0001$) test, and there were no significant differences in albumin $P \leq 0.088$ and cholesterol $P \leq 0.114$ compared patients and healthy.

Table 4.9 Comparison gender and groups control with patient in all studied groups for urea, creatinine, albumin, and cholesterol

Gender	Groups	Mean (mg/dL) ± SD				N
		Urea Test	Creatinine	Albumin	Cholesterol	
Male	Control	30.21b ± 8.56	1.01b ± 0.25	3.81a ± 0.36	150.63a ± 30.24	19
	Patient	78.36b ±10.21	1.01b ± 0.24	4.07a ± 0.43	195.36a ± 35.72	11
Female	Control	35.12a ± 38.01	1.34a ± 2.36	4.06a ± 0.42	152.76a ± 28.43	33
	Patient	158.58a ± 41.46	6.96a ± 2.25	3.87a ± 0.36	190.53a ± 45.51	19
P value		0.0001	0.0001	0.088	0.114	82

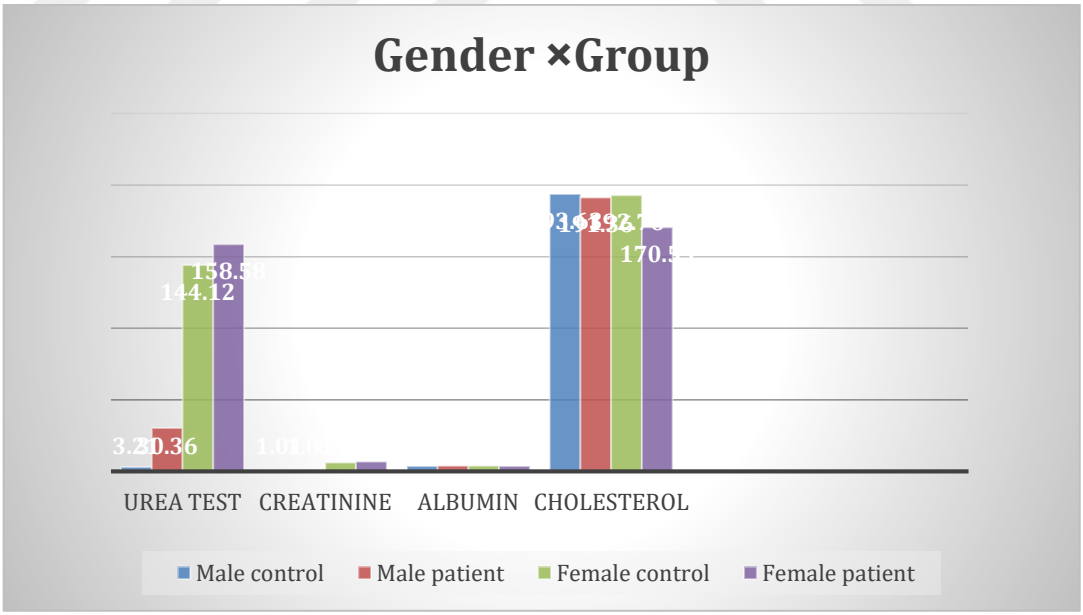

Figure 4.9 Comparison gender and groups in all studied groups

The results in Table 4.10 and Figure 4.10 showed a significant difference P ≤ 0.0001 in the concentration of total antioxidants and a significant difference in CoanzimQ10 and P≤0.0004 respectively between males and females with patients and healthy controls.

Table 4.10 Comparison gender and groups in all studied groups

Gender	Groups	Mean (mg/dL) ± SD		N
		Total antioxidant	CoanzQ10	
Male	Control	1.24b ± 0.13	0.86b ± 0.70	19
	Patient	1.22b ± 0.14	0.92b ± 0.69	11
Female	Control	1.56a ± 0.25	1.45a ± 0.77	33
	Patient	1.67a ± 0.28	1.85a ± 0.78	19
P value		0.0001	0.0004	82

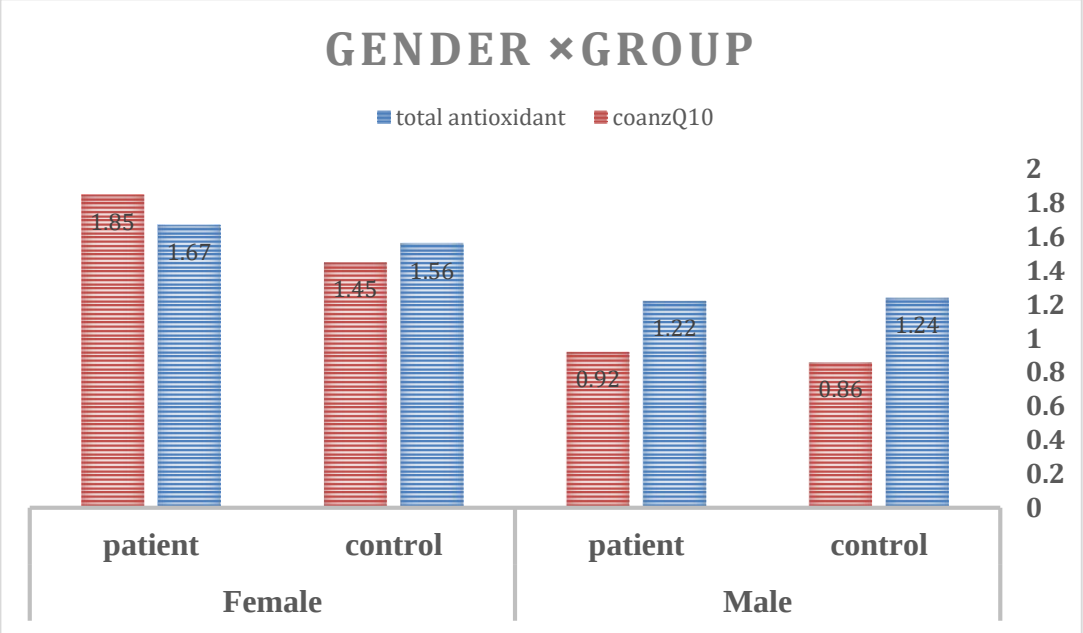

Figure 4.10 Comparison gender and groups in all studied groups

5. CONCLUSSIONS

Renal failure refers to the inability of the kidneys to perform the excretory function resulting in the retention of nitrogenous wastes from the blood, Kidney functions and through our study, an attempt to find the relationship between coenzyme Q10 as well as antioxidants in patients, as well as studying the relationship between some biochemical variables with total antioxidants and coenzyme help.

5.1 Demographic and Clinical Characteristics of the Study Groups

The results of the present study show that there is a significant increase in the levels of urea and creatinine in the blood compared to the healthy control in patients with chronic kidney disease, the results are in agreement with a previous study (Barros *et al.* 2005), in which toxin retention was found to be an important contributor to the development of uremia in patients with advanced CKD and ESRD (De Mauri *et al.* 2020). The results showed a significant increase ($P \leq 0.0001$) in antioxidants, and coanzQ10 in CRF patients, respectively with the control group.

In addition, the results refers that there is no significant difference in the concentration of creatinine, urea, albumin, and cholesterol between males and females in CRF, respectively, compared to the control group, it is in agreement with the present study, while it is not significant for albumin level at age (70 - 80), this results are in agreement with previous studies.

5.2 Serum Urea and Creatinine

Chronic Kidney Disease (CKD) is a progressive reduction in renal function (Borrego-Utiel 2020). Serum urea and creatinine are most widely accepted parameters to assess Chronic Kidney Disease (CKD) status as well as to assess renal status in susceptible diabetic and hypertensive subjects. The results of the present study shows that there is a

significant increase in the levels of serum urea, creatinine when compared to control group with CKD, these results are in agreement with previous study (Barros *et al.* 2005), who found that, toxin retention has been considered as a significant contributor to the development of uremia in patients with advanced CKD and ESRD (De Mauri *et al.* 2020).

When renal function is impaired, increasing concentrations of blood urea will steadily accumulate. For a long time, urea has been considered to have negligible toxicity. However, the finding that plasma urea is the only significant predictor of aortic plaque area fraction in an animal model of chronic renal failure -accelerated atherosclerosis, suggests that the high levels of urea found in chronic dialysis patients might play an important role in accelerated atherosclerosis in this group of patients (Zhang *et al.* 2014). Urea has long been thought to be biologically inactive, as a measure of uremic retention in chronic kidney disease (CKD) and the effectiveness of intradialytic solute removal (Vanholder *et al.* 2018). The advancement of kidney damage is marked by an increase in two essential chemical compounds in the blood: creatinine and urea, which are measured in serum to determine GFR and then renal function. Creatinine and urea, on the other hand, are not directly harmful and are solely used to assess kidney function. These findings corroborate those of Chris Higgins, who demonstrated that kidney illness is linked to decreased urea excretion and, as a result, a rise in blood concentration. Urea is a metabolic waste product that is expelled in urine by the kidneys. Kidney disease is linked to a decrease in urea excretion and, as a result, a rise in blood urea concentration (Saral *et al.* 2019).

5.3 Albumin and Cholesterol

In the early stages of CKD, plasma triglyceride concentrations rise to their greatest levels. Levels in nephrotic syndrome patients on hemodialysis (Lentine *et al.* 2012). Rate in affected patients, the ratio of triglycerides to cholesterol in LDL and HDL particles is also higher.

Hypertriglyceridemia [G] is caused by a delay in triglyceride catabolism in CKD. Decreased LCAT activity is associated with rich lipoproteins, such as VLDL particles and chylomicron [G] residues.

The results showed that there is no significant increase ($P \leq 0.088$) in albumin and cholesterol ($P \leq 0.114$). While there was an increase in albumin compared to age, some cases may have been missed in our research. Finally, further studies must be conducted to reach an outcome. The patients studied were also taking antibiotics (ceftriaxone) and calcium, which affected accurate results given the duration of follow-up in this study, which was conducted during the patient's stay in the hospital.

The same concentration or little change in albumin and cholesterol appeared in the same group. Chronic kidney disease (CKD). There are no statistically significant differences in the albumin levels observed in the patient when compared to the healthy control. Also, there are no statistically significant differences in the patient's cholesterol levels when compared with the healthy control.

5.4 Coenzyme Q10

Coenzyme Q10 (CoQ10) is a fat-soluble vitamin-like Quinone, also known as ubiquinone, that exerts ant oxidative functions. CoQ10 transports electrons from complexes 1 or 2 to complex 3 in mitochondria (Garrido-Maraver 2014).

The results showed that there was a significant increase in the concentration of the coanzimQ10 in patients with CRF respectively compared with the control group which coq10 ($P \leq 0.0004$). Therefore, it has been found an apparent difference between them and through the values of ($P \leq 0.0004$), it is in agreement with previous study (Lu *et al.* 2020).

There are some evidence that CoQ10 supplementation may improve renal function and reduce the need for dialysis in patients with CKD. In a randomized controlled study (Chang and Singh 2000), 97 CKD patients were given supplementary CoQ10 (3 x 100mg daily for 3 months) or placebo. There was a significant improvement in markers of renal function (e.g. serum creatinine) in CoQ10 supplemented patients compared to placebo, in both dialyzed and non-dialyzed patients. In particular, the number of patients requiring dialysis in the CoQ10 treated group decreased from 21 to 12, whilst remaining unchanged at 24 in the placebo group. In an animal model of CKD, the reduced form of CoQ10, ubiquinol, was found to decrease kidney superoxide levels as well ameliorating renal dysfunction (De Jong *et al.* 2008).

At present, there are no studies that have assessed the CoQ10 status of normal human renal tissue due to the invasive nature of kidney biopsy. However urinary tract CoQ10 analysis could be an appropriate approach for assessing kidney CoQ10 status, and may help fulfill the critical need for less invasive procedures to determine tissue CoQ10 status. Recently, a new methodology for the measurement of CoQ10 in urine has been standardized, including the establishment of reference values for a pediatric control population (Yubero and Larrañaga 2015).

This new evaluation of urinary tract CoQ10 is a non-invasive procedure that might be useful for estimating CoQ10 kidney status for diagnosis and especially for CoQ10 treatment monitoring. The results obtained in this study cannot be extrapolated to this population. Occasionally, asymptomatic acute kidney injury may occur in patients after hospital discharge (Patzer 2008), Some cases may have been missed in our search since individuals with renal failure were discovered to take antibiotics (ceftriaxone) and calcium, impacting accurate results given the length of follow-up in this investigation, which was completed throughout the patient's stay in the hospital. Finally, more research with varied doses and durations of CoQ10, as well as examination of other AKI indicators such IL-18, KIM-1, L-FABP, and Cystatin-C, is recommended.

5.5 Antioxidant

Oxidative stress is the imbalance between the rate of production and removal of produced oxidants. In other word it is an increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) and/or decrease in endogenous/exogenous antioxidants. It is the causative factor of a wide variety of diseases such as neurodegenerative diseases, diabetes, atherosclerosis, ischemia, and kidney disease (Rafieian-Kopaei 2013).

The results shown a significant increase ($P \leq 0.0001$) in the concentration of antioxidants, between patients and the control group, it found an apparent difference between them and through the values of ($P \leq 0.0001$), it is noticed in the present study that patients with renal failure take antibiotics (ceftriaxone) and calcium, which affects the accurate results in light of the follow-up period in this study that was conducted. During a patient's stay in the hospital, some cases may not have been missed in our research. Finally, further studies with different doses and duration of antioxidant administration are recommended as well as analysis of other biomarkers of AKI such as IL-18, KIM-1, L-FABP and Cystatin-C. Oxidative stress is frequently observed in CKD/ESRD and is a non-traditional risk factor for all causes of mortality (Rysz *et al.* 2020).

For this reason, oxidative stress has become an important diagnostic and prognostic factor and is a target for CKD prevention/treatment. High levels of oxidative stress have already been found in the early stages of CKD (Gui *et al.* 2021). Which increase in parallel with the progression to ESRD (Roumeliotis *et al.* 2021), and is further exacerbated in HD patients (Wertz *et al.* 2020). ESRD patients on peritoneal dialysis (PD) have increased oxidative stress, when compared to non-dialyzed uremic patients (but lower, when compared to HD patients) (Rysz *et al.* 2020). In fact, HD and PD have both been shown to increase oxidative processes, leading to an increase in the state of oxidative stress. Moreover, oxidative stress may also persist after renal transplantation. Oxidative stress has also been linked to the production of highly reactive intermediates during inflammation; on the other hand, reactive oxygen species (ROS) are able to further enhance the inflammatory response by triggering pro-inflammatory mediators (e.g., NF-

B). Low amounts of pro-oxidative agents, which have important defensive roles, are normally produced by cells but are inactivated by enzyme systems (e.g., glutathione) and other antioxidants (called scavengers) for their ability to neutralize free radicals. In the kidneys, ROS are mainly produced by the mitochondrial respiratory chain and by enzymes such as NAD PH oxidase (NOX). The di errant NOX isoforms, including NOX_1, NOX_2 and NOX_4, are mainly responsible for oxidative stress, worsening vascular function and promoting fibrosis (Ning *et al.* 2021).

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APPENDICES

APPENDIX 1. ELISA (enzyme linked immunsorbent assay)

APPENDIX 2. Selecta prom (kidney function analysis)

APPENDIX 3. Otomatik pipette

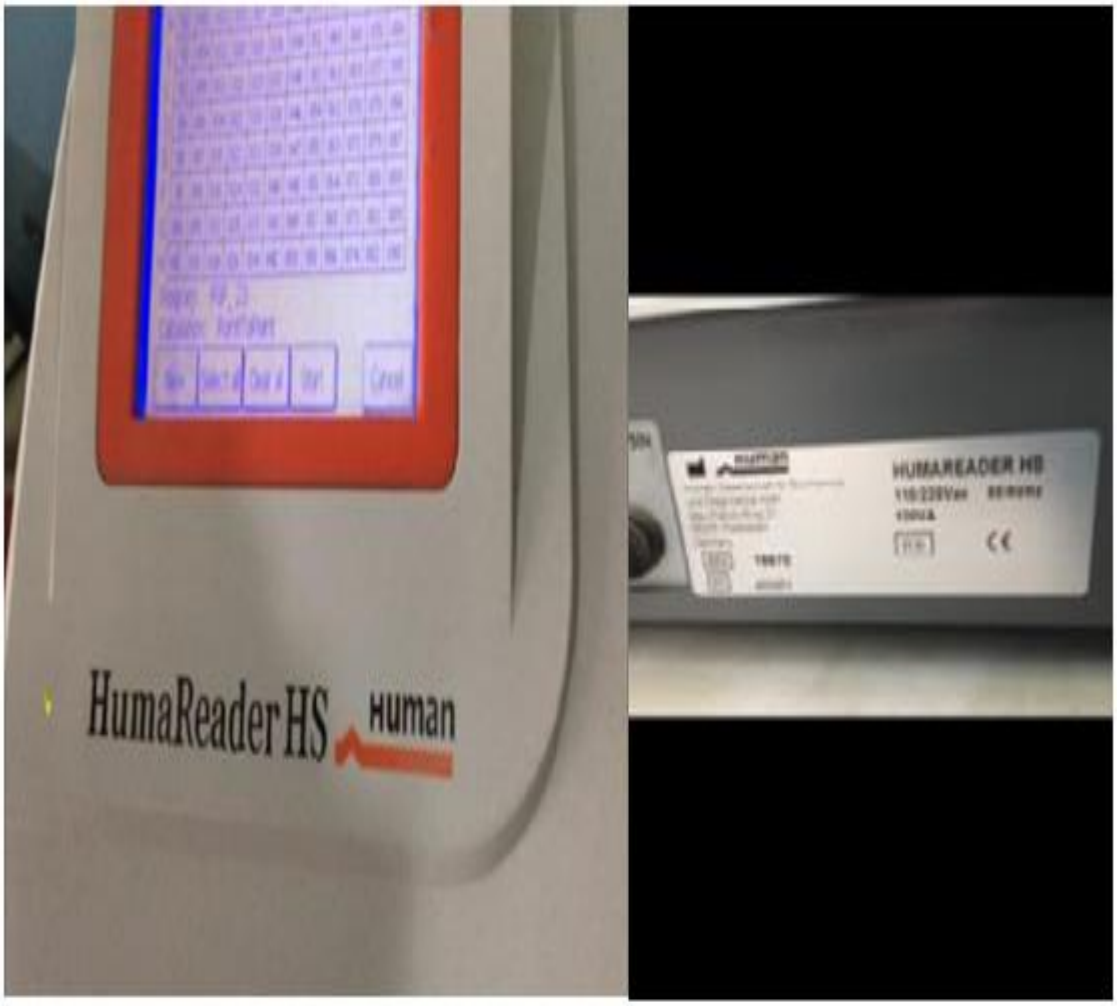
APPENDIX 4. Redused glutathion (GSH)

APPENDIX 5. Lt contains a substance that helps blood clotting

APPENDIX 6. Centrifuge

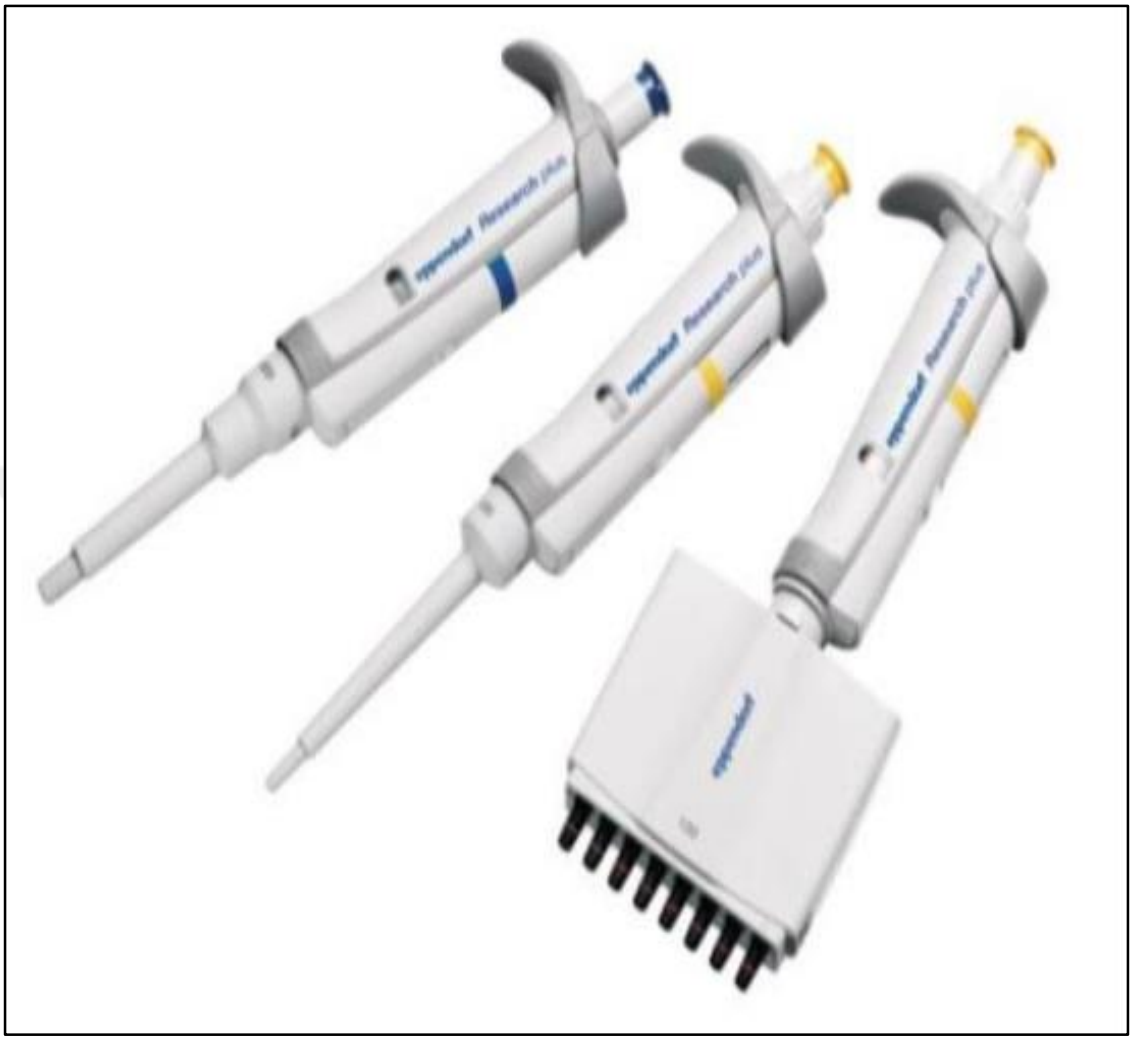
APPENDIX 7. Thermo scientific

APPENDIX 1. ELISA (Enzyme Linked Immunsorbent Assay)

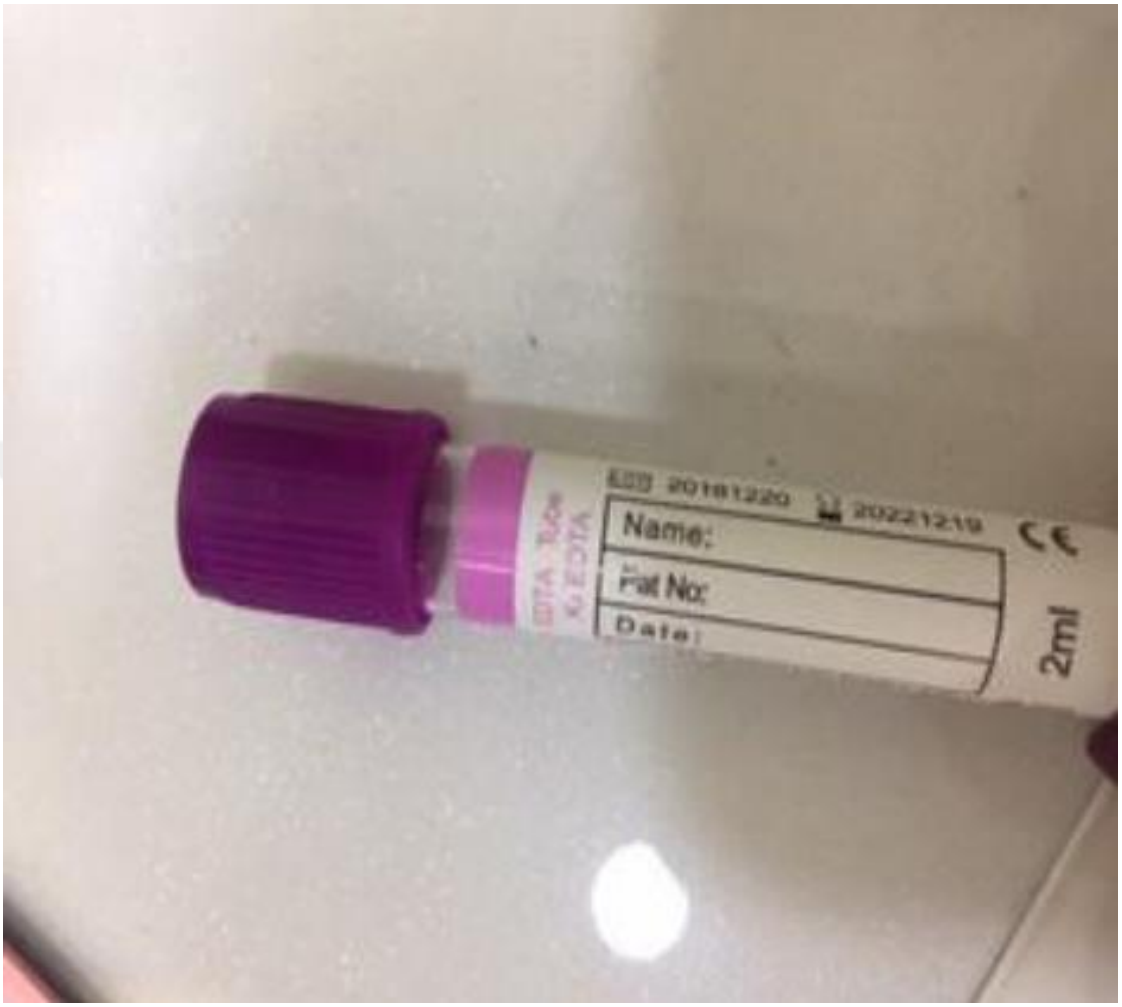


APPENDIX 2. Selecta prom (kidney function analysis)

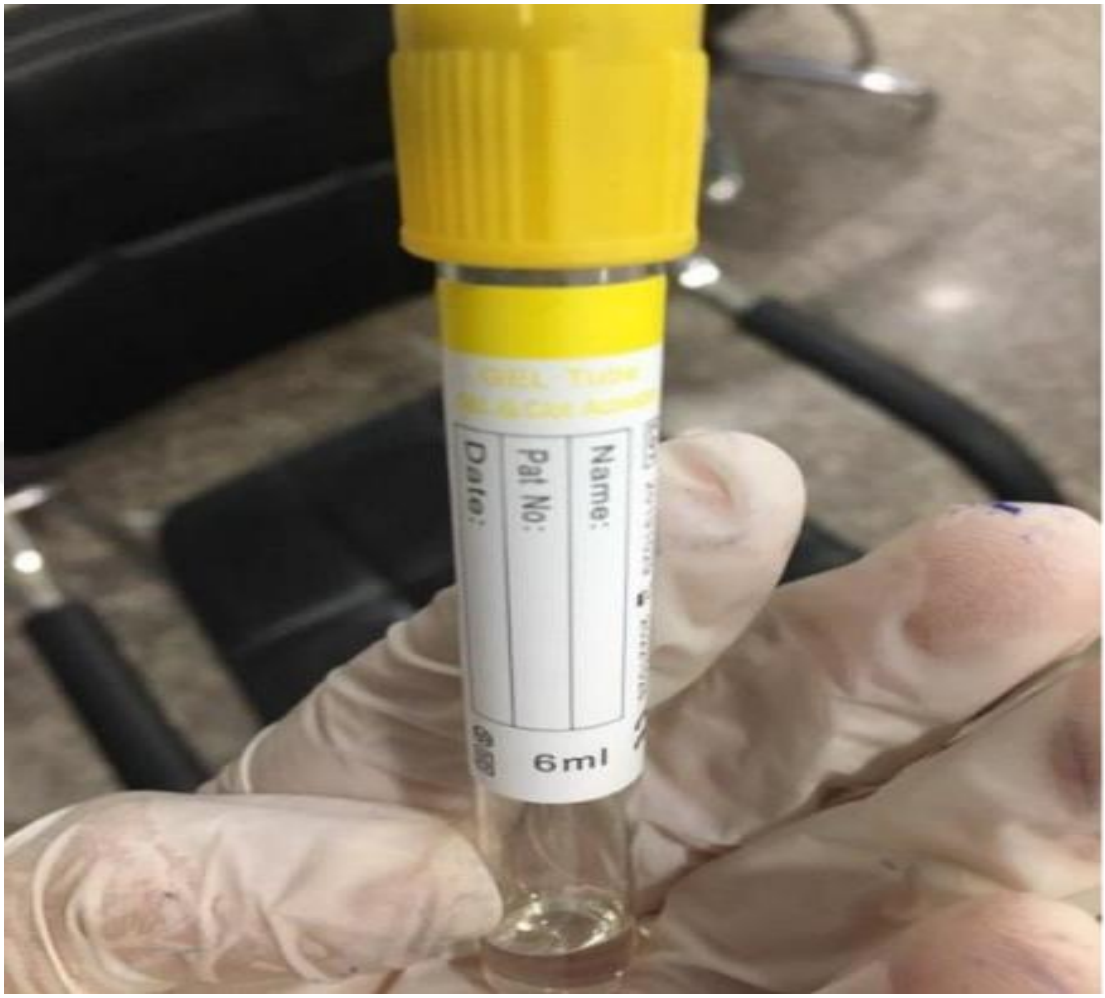
APPENDIX 3. Otomatik pipette



APPENDIX 4. Edta Tube



APPENDIX 5. Lt contains a substance that helps blood



APPENDIX 6. Centrifuge

APPENDIX 7. Thermo Scientific

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