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Effects of L-carnitine on some parameters in patient with chronic kidney disease

A Thesis

Submitted to the Council of College of Education for Pure Sciences/ University of Karbala /in Partial Fulfillment of the Requirements for the Degree of Master in Chemistry Sciences

By:

Eirteham Saeed Raheem

Supervisors

Asst. Professor Dr. Rehab Jasim Mohammed

Professor Dr. Ali Jasim Muhaimid Al-Sultani

(2023 A.D) **(1445 A.H)**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

«وَإِذَا مَرِضْتُ فَهُوَ يَشْفِينِ»

الآية (٨٠) من سورة الشعراء

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Signature:

Supervisor

Assist. Prof

Dr. Rehab Jasim Mohammed

Address: Department of chemistry

College of education for pure

University of Karbala

Date: / / 2023

Signature:

Co Advisor

Nephrology and internal medicine

Dr. Ali Jasim Muhaimid

Address: Department of Dialysis

College of Medicine

Hospital/Babli/Iraq

Date: / / 2023

Signature:

Name: Dr. Sajid Hassan Guzar

Address: Head of the chemistry department

University of Karbala

Date: / /2023

Committee Certification

We attest that we have read the following thesis (**Effects of L-carnitine on some parameters in patient with chronic kidney disease**) and as the student was scrutinized by the examining committee (**Eirteham Saeed Raheem**) that it is appropriate in terms of substance and in our judgment as a thesis for the degree of Master of Chemistry

Signature: (Chairman)

Name: Prof. Dr. Rana Fadhil Mousa

Address: University of Kerbala

Date: / /2023

Signature: (Member)

Name: Asst. Prof. Dr.

Ali Nouri Fajar

AbbasAddresس: University of Qadisiya

Date: / /2023

Signature: (Member)

Name: Asst. Prof. Dr.

Suzanne Jubair

Address: University of Kerbala

Date: / /2023

Supervisor (Member)

Assist. Prof.

Dr. Rehab Jasim Mohammed

Address: University of Kerbala

Date: / /2023

Co Advisor (Member)

Nephrology and internal medicine

Dr. Ali Jasim Muhaimid

Address: Department of Dialysis

Date: / /2023

Approved by the college's graduate studies committeeSignature:

Name: Prof. Dr. Hameedah Idan Salman

(Dean of the college)

Date: / /2023

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I confirm having read the thesis titled (**Effects of L-carnitine on some parameters in patient with chronic kidney disease**), by (**Eirteham Saeed Raheem**), and have rectified every grammar error I discovered. It can thus be discussed by the examination committee.

Signature: 

Name: Dr. Shaima Abdel-Amir Karim

Address:

University of Karbala

Date: / /2023

Certification by scientific

I attest that this thesis (**Effects of L-carnitine on some parameters in patient with chronic kidney disease**), by **(Eirteham Saeed Raheem**), was evaluate it scientifically and present it for consideration.

Signature: 

Name: Asst.Prof.Dr.

Amer Hassan Abdullah

Address:
University of Al mustansiriyah

Date: / /2023

Signature: 

Name: Asst.Prof.Dr.

Manal Farhan Mohsen

Address:
University of Kufa

Date : / /2023

Dedication

To my mother and father, may God preserve their health, extend their lives, and fill them with happiness in this world and victory in the Hereafter.

To that great man who brought out the best in me and always encouraged me to reach my ambitions, to the symbol of achievement, and to the companion of my life... my dear husband, may God protect him from all evil.

To my brothers, sisters and friends, may God protect them

To everyone who taught me a letter throughout my educational career and enlightened me on the path of knowledge and knowledge

I dedicate this work as a candle in the paths of knowledge, and God is the guardian of success.

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7- Finally, I would like to thank the of patients who participated in the study and wish them a speedy recover.

Summary

This study was conducted to investigate the effect of L-Carnitine on chronic renal failure patients undergoing dialysis. The study included 40 patients, aged between (21-62) years. The study was divided into two phases, the first phase (pre-use of treatment) and the second phase (post-use). L-Carnitine Extra treatment was given to dialysis patients at a dose of (1600) mg per day orally for a period of three months. Samples were taken from Imam Al-Sadiq Teaching Hospital in Babli Governorate, Division of the Industrial College (dialysis) during the time period from 14/8/2022 (August) to 4/3/2023 (March), where parathyroid hormone (PTH) was measured by ECLIA technique and using COPA immunoassay analyzer device from Roche company in Switzerland, calcium and phosphorus were measured by spectrophotometer, albumin was measured by Human Star 300SR device in France, hemoglobin was measured by CBC Cell Tac device in Japan, and CK enzyme was measured by Fujifilm device in Japan.

In the results of the statistical analysis, the study concluded that there is a significant difference in parathyroid hormone, calcium, phosphorus, albumin, hemoglobin, and creatine kinase enzyme in dialysis patients after using the treatment compared to the pre-treatment stage, where we noticed a decrease in the level of PTH, PO4, and CK enzyme after treatment, and an increase in their Ca, albumin, and hemoglobin levels compared to what they were before treatment.

The results of the study also showed that the treatment had a clear effect on the level of vital parameters for dialysis patients with a shorter period of time (the duration of the disease is less than three to six months), as well as patients who had fewer dialysis sessions per week than (1-2) times per week.

During this study, patients who were treated with L-Carnitine commented that they felt an improvement in their health and noticed an improvement in their ability to walk long distances and an increase in physical endurance, in addition to their ability to reduce the number of hours of dialysis session, which they were not able to do before using the treatment.

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Abbreviations

ADP……. Adenosine Di Phosphate
ATP ……. Adenosine Triphosphate
CK……. Creatine Kinase
CKD…… chronic kidney disease
CRF……...Chronic Renal Failure
DNA …… Deoxyribonucleic Acid
FDA…… Food Drug Administration
GFR……. Glomerular Filtration Rate
GTP ……. Guanosine Triphosphate
HBA ……. Hemoglobin Subunit Alpha
HBB ……. Hemoglobin Subunit Beta
HD……...…. Hemodialysis
LDL…… Low-Density Lipoprotein
NADP ……Nicotinamide Adenine Dinucleotide Phosphate
OCTN……. Organic Cation Carriers
PCD……. Primary Carnitine Deficiency
PTH…… Parathyroid hormone
RNA…… Ribonucleic Acid

CHAPTER ONE

INTRODUCTION

1.1. Kidney

The kidney is an important organ of the body with a length of about 12 cm. The kidneys are located in the upper posterior part of the abdominal cavity behind the posterior peritoneum on either side of the spine and below the diaphragm. The human body contains two kidneys, one on the right side, and it is smaller than the left kidney adjacent to the spleen, due to the location of the liver. The kidneys get a large amount of the blood that the heart pumps, about 20% through the aorta, even though they make up only 5% of the body mass [1]. Each kidney is surrounded from the outside by a capsule, which is a thin, smooth capsule of connective tissue that serves to protect the kidney from trauma [2].

One kidney contains more than a million nephrons, and the nephron is considered the structural and functional unit of the kidney. Each nephron contains a filter known as the glomerulus that allows fluids and water to pass into the tubules. Large molecules such as proteins and blood cells remain in the blood vessel. The second part of the nephron, which forms an independent functional unit, is known as the renal tubule. Its function is to extract urine and toxins from blood plasma, as well as the process of forming urine [3].

Nephrons carry out their work in two stages, filtering and cleaning the blood in the glomeruli, and then reabsorbing many important substances that the body needs, such as amino acids, glucose, and others as show in the following figure.

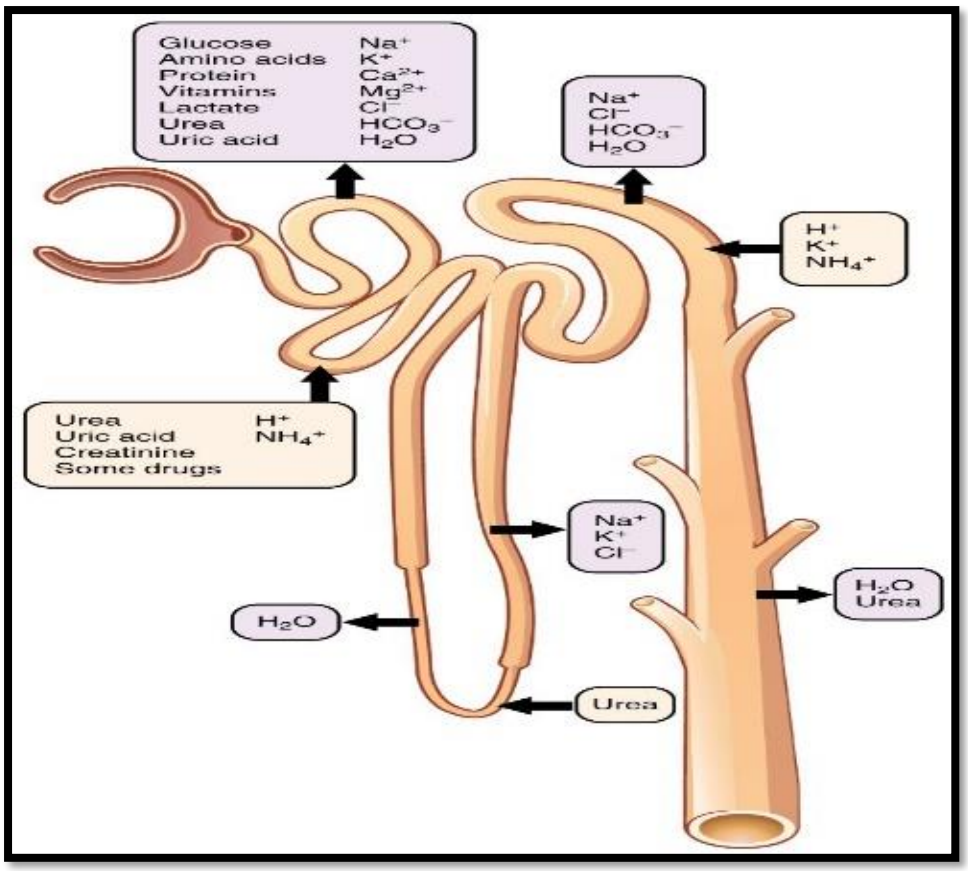

Fig. (1-1): Excretion and Reabsorption of Various Substances Through the Kidneys [4].

In the event of kidney Injury (nephron damage) the kidney has the ability to maintain the glomerular filtration rate through excessive filtration and compensatory inflation of the remaining, non-disease nephrons for a period of time, but if the damage continues for a longer period, more nephrons are closed, so the remaining nephrons cannot filter the blood well, which leads to a decrease in kidney function, and this Is called renal failure, which affects the entire body [5].

1.1.1. Function of Kidney

The primary function of the kidneys is to filter blood, rid the body of waste, and form urine, in addition to its work as endocrine glands, it secretes a group of basic hormones that control the organs of the body [6,7].

1.1.1.1. Basic Kidney Function

One of the most basic functions of the kidneys:

1- Elimination of waste, especially compounds resulting from the breakdown of proteins (nitrogen compounds) such as urea and creatine.

2- Getting rid of excess fluids the kidneys regulate the number of fluids and water in the body as they work to filter about (200 liters) daily of fluids and get rid of (1.5-1 liters) of urine.

3- Mineral balance the kidneys play an Important role in regulating the electrolyte elements (sodium, potassium, calcium, etc.) of ions and salts.

1.1.1.2. Kidney Functions as Endocrine Glands

The kidneys act as endocrine glands by secreting a group of essential hormones:

1-Controlling blood pressure by producing a group of hormones that help regulate blood pressure and control calcium metabolism, such as (renin, aldosterone).

2-The production of red blood cells through the hormone erythropoietin, which stimulates the formation of red blood cells in the body [8].

3-Converting vitamin" D" Into its active form, which is necessary to absorb calcium from food and maintain healthy bones and teeth as show in the following figure.

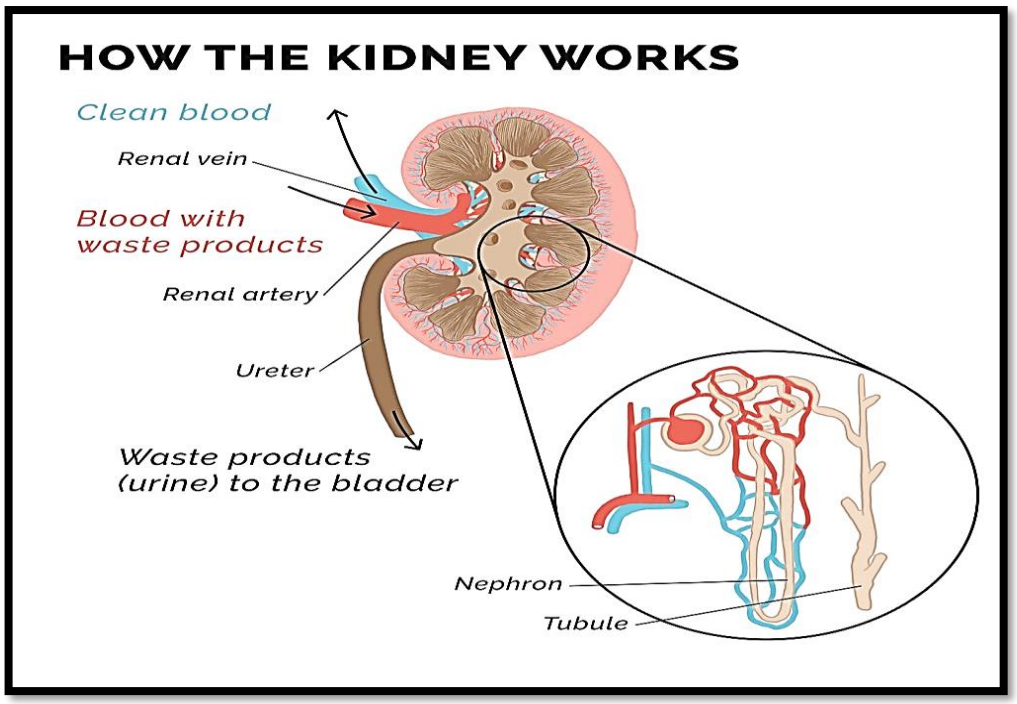

Fig. (1-2): Basic Structure of the Kidney [9].

1.2. Renal Failure

Renal failure is a medical condition resulting from a defect in the function of the kidneys and its inability to rid the body of waste, maintain the internal balance of water and mineral salts, purify the blood from Impurities, and other vital functions [10].

Renal failure is a disease that has several different symptoms and signs, resulting from many causes. It leads to a decrease in the glomerular filtration rate and the accumulation of waste in the tissues of the body It was called in the past "urinary poisoning"[11, 12].

1.2.1.1. Types of Renal Failure: -

There are two types of kidney failure:

- Acute renal failure and occurs within a few hours or days (cases that develop rapidly) and is caused by a decrease in the rate of urination to less than (30 ml / hour) and the matter may develop into complete non-excretion of urine.
- Chronic renal failure and this begins with a gradual deterioration in kidney function over months or years and in several stages, which is the last stage of kidney failure, which leads to kidney damage and its Inability to perform Its vital functions [13, 14,15].

1.2.1.2. Chronic Renal Failure (CRF)

Chronic kidney disease is one of the main health problems common all over the world, especially in patients with diabetic kidney disease and glomerulonephritis [16].

Chronic renal failure is defined as a clinical condition characterized by irreversible loss of kidney function and dysfunction in the functional units of the kidneys (nephrons) resulting from the Inability of the kidneys to perform their vital functions [17].

In chronic renal failure, kidney function decreases to less than 25% of its normal level, and more than 95% of the various kidney tissues are destroyed, which leads to an increase in the accumulation of metabolic waste (resulting from catabolism and cellular building) and an increase in fluids and urea. The kidneys also lose part of their physiological activity and this leads to the accumulation of fluids and toxins in the body [18].

1.2.1.3. Causes of Chronic Renal Failure

These diseases, conditions, and factors may damage the kidneys and cause chronic kidney failure:

1. Long-term, irreversible acute renal failure or as part of a disease progression eventually causing chronic renal failure.
2. Long-term obstruction of the urinary tract due to an enlarged prostate gland, cancer, or kidney stone [19, 20].

3. Metabolic syndrome, a group of problems that occur together, increases the risk of heart disease, stroke, and type 2 diabetes [21].
4. Diabetes mellitus of both types which causes disruption of the renal filtration system resulting from damage to the vessels inside the kidneys.
5. High blood pressure, where repeated high pressure more than 14/9 mm Hg, leads to atrophy of the cortex of the kidneys due to narrowing of the arteries feeding the kidneys [22].
6. Other causes such as kidney stones, acute or chronic kidney infection, obesity [23, 24].
7. Pre-kidney operations (low renal perfusion pressure), intrinsic kidneys (diseases of the arteries, interstitial tubes, or glomeruli), or post-kidney operations (obstruction) can also lead to chronic renal failure [25].

1.3. Stage of Kidney Disease

Kidney failure passes through five stages and the patient's stage is determined depending on the percentage of kidney damage and the glomerular filtration rate which is a measure of the level of kidney function as show in the following table [26,27].

Table. (1-1): Chronic Kidney Disease Staging [28].

Chronic Kidney Disease Staging

Stage	eGFR (mL per minute per 1.73 m^2)	Description
1	≥ 90	Normal or increased GFR
2	60 to 89	Mildly decreased GFR
3a	45 to 59	Mildly to moderately decreased GFR
3b	30 to 44	Moderately to severely decreased GFR
4	15 to 29	Severely decreased GFR
5	< 15 or dialysis	End-stage renal disease

- In the Initial stages, in which the glomerular filtration rate is between (90-60 ml /min), the patient does not show any symptoms of the body's ability to deal with the decline in kidney function. Usually, some signs indicating mild damage to the kidneys (presence of protein in the urine, swelling of the legs, high blood pressure, diabetes, etc.) In these stages, the disease is treated with medications such as blood pressure medications, diuretics, vitamin D, and others [29,30].
- In the advanced stages, in which the glomerular filtration rate ranges from (30 to less than 15 ml/min), a group of symptoms appears on the patient, including (poor appetite, gastrointestinal disorder, muscle spasm, little or no urination, and anemia [31,32].

Which is one of the most important complications that accompany a patient with chronic renal failure and are caused by a defect in the production of the hormone erythropoietin), and the patient may suffer from itching, changes in skin color and increased skin pigmentation. In these stages, the patient needs a kidney transplant or undergoing dialysis, the most famous of which is dialysis, which works to remove waste and fluids from the body and get rid of nitrogenous substances and purify the blood by the dialysis machine [33, 34,35].

1.4. Dialysis

A medical procedure that aims to remove waste, toxic substances and excess fluids from the body when the kidneys stop working properly due; to chronic kidney disease.

Dialysis is the only way through which the patient can be saved in the event that the kidneys are unable to filter the blood sufficiently, as it helps in controlling blood pressure and achieving a balance between important minerals such as sodium, potassium, calcium and phosphorus, but this method does not restore the damaged kidneys, but only performs its function [36].

A patient with renal failure in his last stage needs dialysis when he loses about (85-90%) of kidney function and the glomerular filtration rate is less than (15 ml / min) In addition to the appearance of a group of symptoms on the patient, including vomiting, feeling tired, and swelling and others [37].

Dialysis is used as a long-term treatment or as a temporary measure until a chronic kidney failure patient can receive a kidney transplant. There are two types of dialysis, and each has its pros and cons. Choosing the most appropriate type depends on:-(Medical problems experienced by the patient and age).

1.4.1. Types of Dialysis

Many doctors recommend dialysis for people with kidney failure when blood tests show that it can no longer filter waste products adequately and that the accumulated waste products are causing problems, there are two types of dialysis:

1.4.1.1 Hemodialysis

It is one of the most used procedures for treating chronic renal failure, and it is a technique that is resorted to for the purpose of getting rid of salts, fluids, and excess waste in the blood when the kidneys lose their ability to function completely.

It is done by drawing blood from the patient's body to the washing machine (the Industrial kidney), which is a special device that filters and purifies the blood, after which the blood Is returned to the body through an arteriovenous fistula, which doctors place (an artificial link) between the patient's artery and vein to help draw blood [38, 39].

This technique helps control blood pressure and maintain the balance of levels of some important minerals in the blood, but it is not considered a definitive treatment for chronic renal failure, it only helps the patient to live longer as show in the following figure.

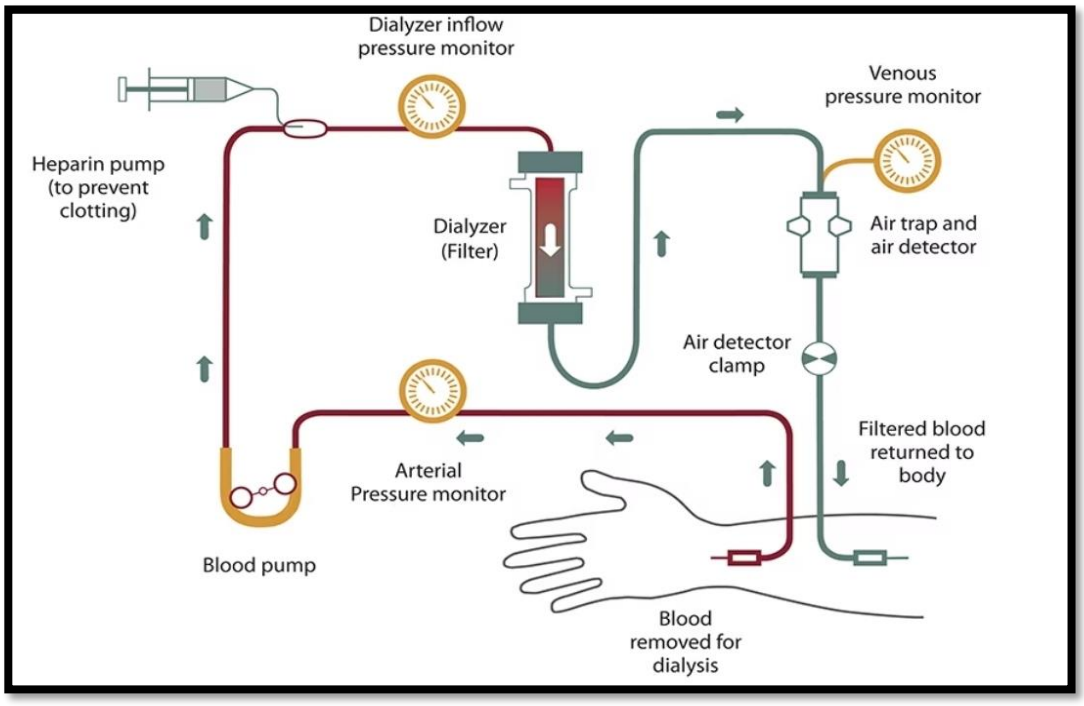

Fig. (1-3): Hemodialysis [40].

1.4.1.2 Peritoneal Dialysis

One of the techniques used to treat chronic renal failure is done through the peritoneum (peritoneum) for the purpose of purifying the patient's blood and getting rid of waste (urea and creatine), where the dialysate fluid is pumped into the membrane and comes out after the end of the peritoneal dialysis proses [41,42].

In both cases, the dialysis fluid has special contents of glucose and electrolytes that are able to permeate the blood as show in the following figure.

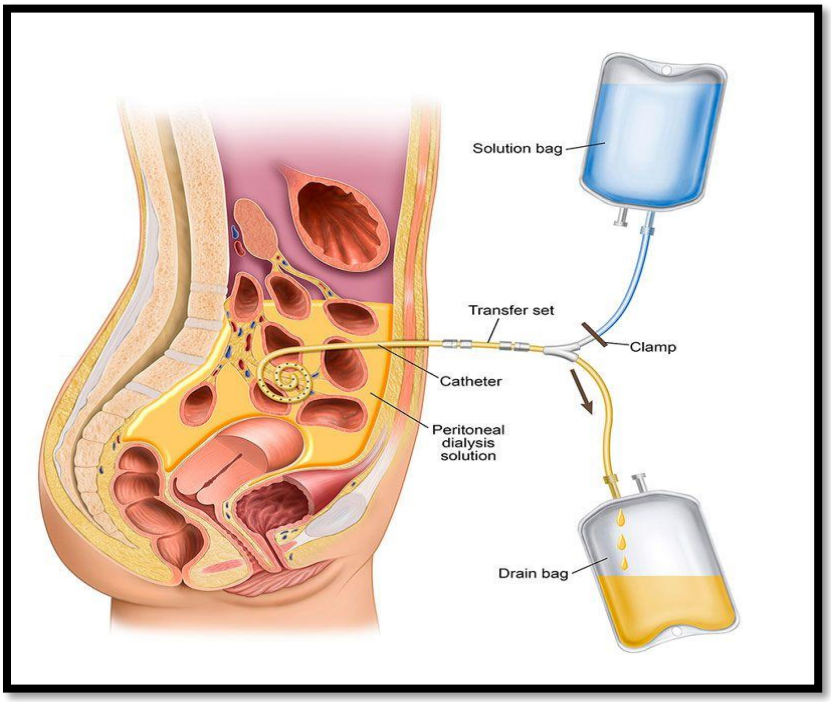

Fig. (1-4): Peritoneal Dialysis (PD) Catheter Illustration [43].

1.5. L-Carnitine

An amino acid nutrient that contains a natural vitamin derived from amino acids and an essential water-soluble molecule that has many functions in the human body L-Carnitine belongs to a quaternary ammonium cationic compound, L-Carnitine compound containing two stereo isomers, the only biologically active L-Carnitine that occurs naturally, and the abiotic D-Carnitine isomer, which is toxic as it inactivates L-Carnitine, as show in the following figure [44].

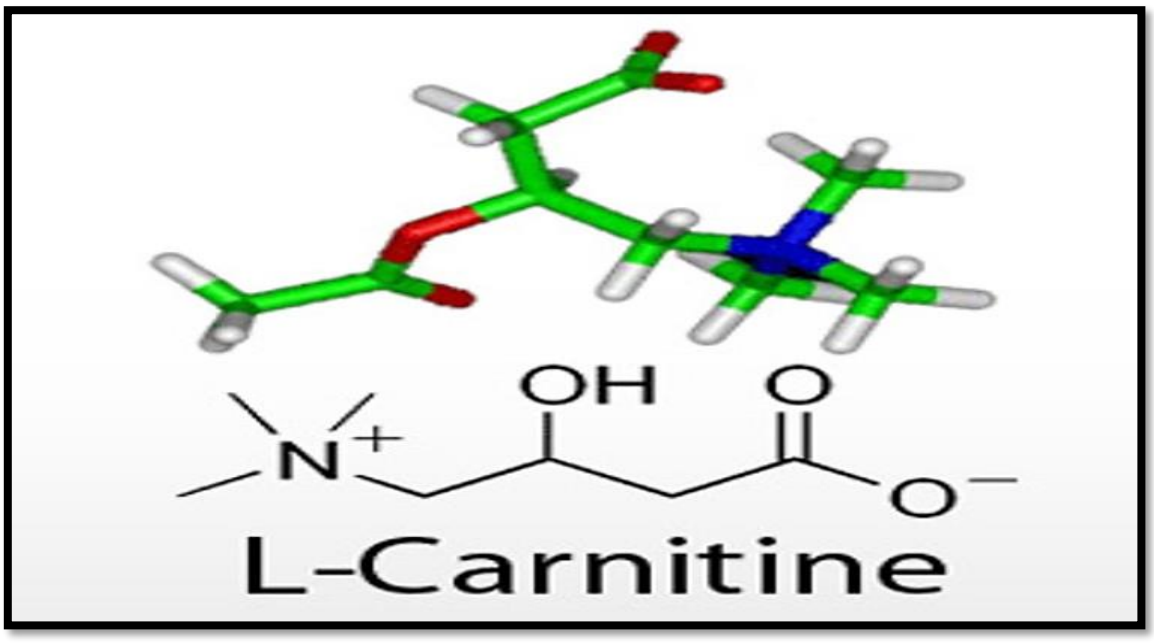

Fig. (1-5): Structure of L-Carnitine [45].

L-Carnitine plays an important role in cellular energy production because it is responsible for transporting long-chain fatty acids from the cytoplasm into the mitochondrial matrix for subsequent degradation via oxidative stress known as the "carnitine shuttle" in the cytosol with three steps:

1. Converting fatty acids present in the form of acetyl-CoA to lipoyl-CoA, and this reaction is very energy, which pushes the inhibition reaction forward.
2. Formation of a long-chain acetyl-carnitine ester to be transported by enzymes of the inner and outer mitochondrial membrane (carnitine palmitoyl transferase 2,1).
3. The latter reaction takes place in the mitochondrial matrix and is catalyzed by carnitine acyltransferase 2 (inner mitochondrial membrane). The carnitine molecule formed is then transported back into the intermembrane space by the same co-transporter (CACT) while lipid acyl-CoA enters into β-oxidation, as show in the following figure.

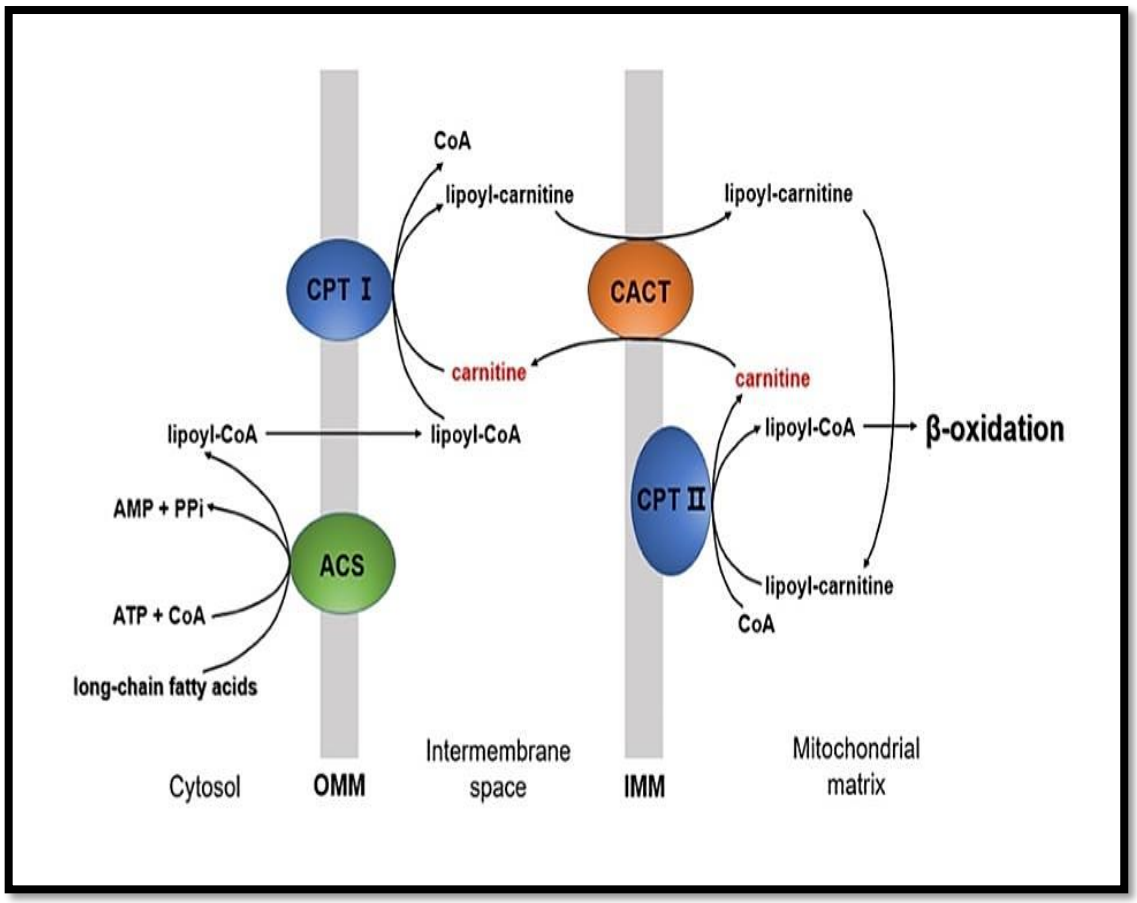

Fig. (1-6): The mechanism by which long-chain fatty acids enter the mitochondria. CPT I, carnitine palmitoyltransferase I; CPT II, carnitine palmitoyltransferase II; ACS, acyl-CoA synthetase; CACT, carnitine-acylcarnitine translocase; OMM, outer mitochondrial membrane; IMM, Inner mitochondrial membrane [46].

L-Carnitine is produced naturally in the body, and its production depends on the extent to which the body eats enough foods that contain the acids lysine and methionine as show in the following figure.

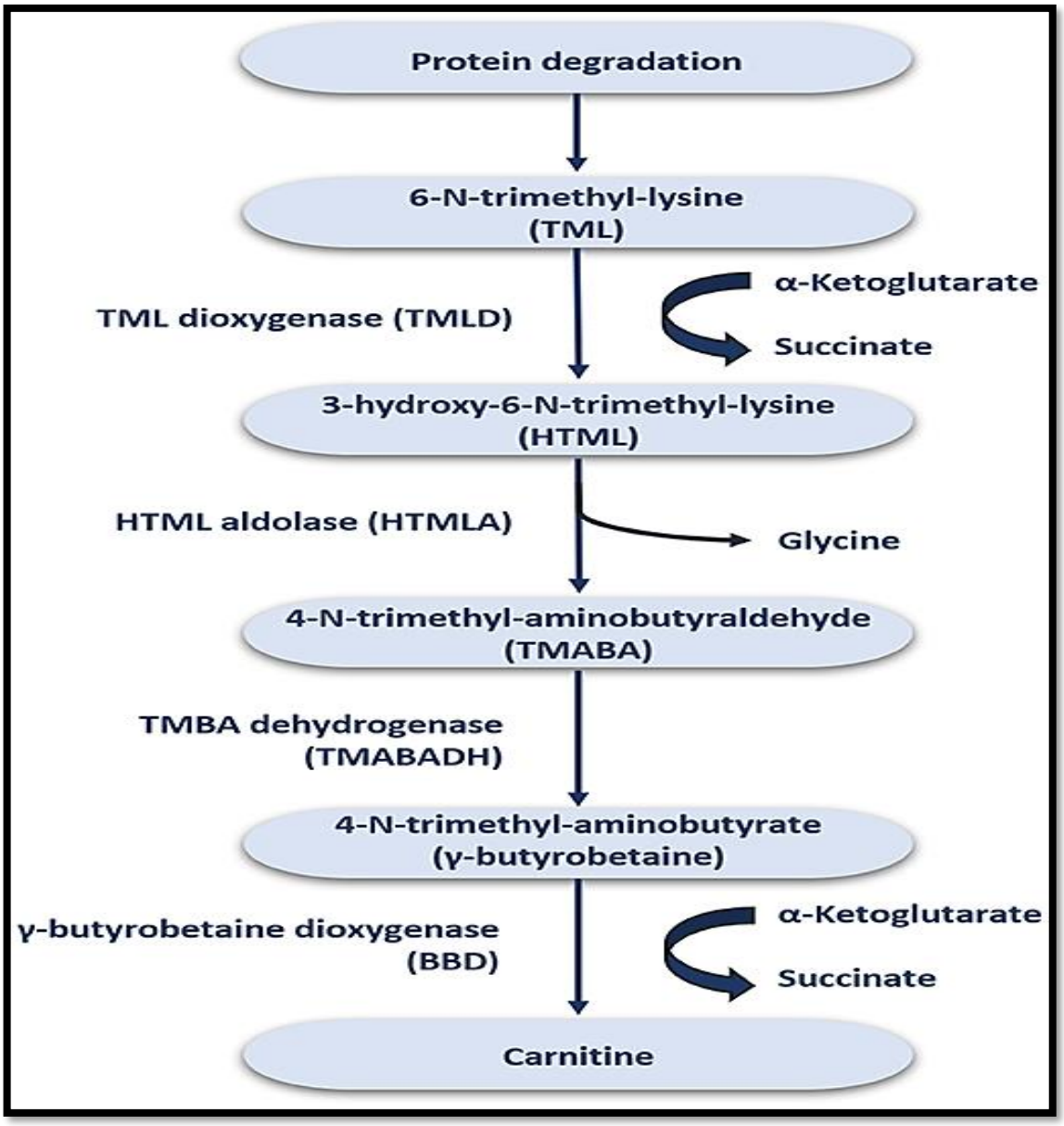

Fig. (1-7): The Endogenous Synthesis of Carnitine [47].

It is estimated that about 75% of the daily requirement of carnitine comes mainly from animal products, fish and dairy products [48], while the remaining 25% is derived from endogenous synthesis.

Under normal circumstances, a person can manufacture (1-2) μ mol Carnitine /kg /day in the human liver, kidneys, testes and brain, therefore, the biosynthesis of L-Carnitine occurs in these sites only [49]. Other tissues, such as skeletal muscles, obtain L-Carnitine from the blood [50].

The distribution and homeostasis of carnitine in the body is controlled by the organic cation transporters OCTN and OCTN2.

OCTN works on intestinal absorption and reabsorption of carnitine by the kidneys and has an important role in tissue distribution by stimulating carnitine to enter cells in the body [51], OCTN2 is the most important physiological L-carnitine transporter due to Its high affinity and wide expression [52].

Loss or mutation of OCTN2 function leads to systemic primary carnitine deficiency (PCD) with severe clinical consequences such as (cardiomyopathy, muscle weakness, hypoglycemia). This type of carnitine deficiency appears at about five years of age [53].

As for the secondary deficiency, it is the result of a group of chronic disorders and diseases, as recent studies have shown that chronic renal failure and liver diseases play an Important role in the deficiency of carnitine.

1.5.1.L-Carnitine and Dialysis

L-Carnitine is indispensable for energy metabolism because it helps activated fatty acids enter the mitochondria, where they are broken down by beta-oxidation. Carnitine is maintained by endogenous synthesis, absorption from dietary sources, and active tubular reabsorption by the kidneys. Healthy kidneys maintain plasma free carnitine levels as show in the following figure [54].

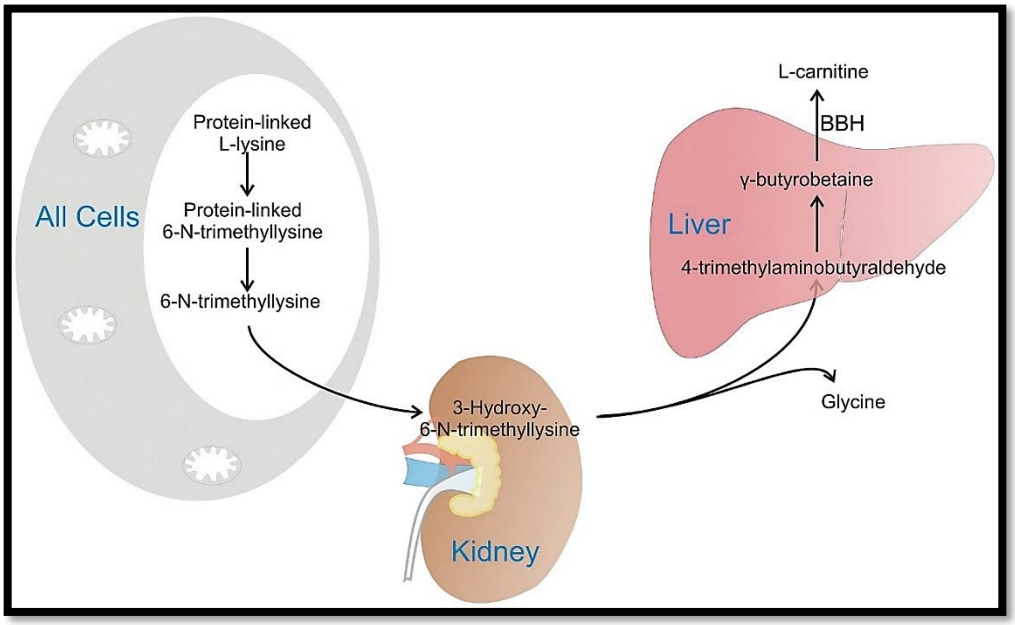

Fig. (1-8): L-Carnitine Biosynthesis [55].

However, in the case of chronic kidney disease, the levels of carnitine in the blood and muscles decrease in patients, especially those who undergo dialysis, as their plasma carnitine concentrations decrease quickly to 40% of their normal level for several reasons: -

1-Decreased carnitine biosynthesis.

2- Low protein Intake as a result of malnutrition [56].

3-Increased clearance and elimination of carnitine by hemodialysis as it Is a water-soluble molecule.

Studies indicate that carnitine deficiency in dialysis patients is one of the important factors that cause several symptoms and complications that appear on the patient, the most common of which are (anemia, irregular heartbeat, irregular blood pressure, etc.) in addition to changing the levels of fats in the blood [57].

Several clinical trials also Indicated that dialysis patients taking high doses of carnitine supplements after each dialysis session could alleviate these symptoms, but this varies from patient to patient [58].

1.5.1.2. Benefits and Properties of L-Carnitine for Dialysis Patients

L-Carnitine is a well-tolerated and safe therapeutic agent in general. It is one of the important drugs that are used to treat and prevent low levels of carnitine in hemodialysis patients. The US Food and Drug Administration (FDA) approved in (1985) the use of carnitine supplements under the trade name (Carnitor). It has been reported that L-Carnitine as a supplement can be beneficial in the treatment of many diseases, including high blood pressure, heart failure, muscle weakness, anemia, chronic kidney disease, and others [59,60], The drug contains an effective substance that occurs naturally within the body and is of great Importance in the performance of many vital body processes: -

1. L-Carnitine is an important catalyst in the metabolism of fatty acids found in the liver, heart and skeletal muscles. It reduces the number of episodes of low blood pressure inside the artery, a shortage of which sometimes occurs in people with hereditary diseases or kidney problems, so it is compensated externally [61, 62].

2. L-Carnitine is an antioxidant that protects the of the body organs from the danger of free radicals that cause some cancerous tumors.

3. L-Carnitine stabilizes the membrane structure of mature red blood cells prolongs their survival, stimulates their formation, and improves the response to erythropoietin through its anti-inflammatory effect, it also works to protect and preserve nerves from damage and destruction, so carnitine is used as an auxiliary factor for red blood cell stimulation factors [63,64].

4. Intravenous administration of carnitine after intravenous dialysis contributes to the replenishment of muscle carnitine levels and the replenishment of removed free carnitine, in cases of diseases of the heart and blood vessels, carnitine is taken orally, as it works to improve the number of red blood cells during dialysis, in addition to Improving heart function in dialysis patients, especially those with left ventricular hypertrophy.

5. Carnitine supplementation significantly reduces levels of LDL cholesterol in the blood, it also improves fatigue through anti-inflammatory activity and antioxidant stress in hemodialysis patients [65,66].

6. Studies have indicated that carnitine supplements are beneficial for dialysis patients, as they contain multiple nutritional supplements that improve many complications, including heart complications and high blood pressure; However, it is not recommended to be given to all dialysis patients, but it is useful for patients suffering from low blood pressure, acute anemia, cardiomyopathy, and muscle spasms [67,68].

1.6. Biochemical Phenotype Parameters

1.6.1. Parathyroid Hormone PTH

A polypeptide hormone also called prohormone. It consists of (84) amino acids. It is mainly secreted by the main cells of the parathyroid glands. Its molecular mass reaches about (9500) Daltons and has a half-life of about (4) minutes [69]. The main function of parathyroid hormone (PTH) is to regulate calcium metabolism in the blood, regulate phosphate in the blood, and synthesize vitamin D. PTH regulates calcium and phosphorus levels in the extracellular fluid and affects Its receptors by stimulating three processes at three sites: -

1. In the bones, PTH releases calcium into the bloodstream through the bones, which reduces the formation of new bone and increases bone destruction.
2. In the intestine, the PTH hormone stimulates the intestine to absorb calcium from food indirectly through its effect on vitamin D metabolism.

3. In the kidneys, the PTH hormone works to reduce the loss of calcium in the urine, in addition to stimulating active vitamin D In the kidneys, as both calcium and vitamin D provide negative feedback to the parathyroid glands [70, 71].

1.6.2. Calcium

Calcium is one of the body s electrolytes and is considered the fifth element after oxygen in terms of natural abundance, when in the form of electrolytes, it plays an important vital role in biochemical processes and physiological functions.

Calcium is an essential element in the metabolism of the cells and is a second messenger affects the function of enzymes and the secretion of many hormones, including insulin [72,73].

Calcium has a structural function. It is an essential element that the body needs in large quantities. Calcium enters the installation and construction of bones and dental and supports the synthesis and function of blood cells.

Calcium regulates blood clotting, nerve transmission, and muscle contraction. Calcium can play all these roles through its ions, which form stable coordination complexes with a group of organic compounds, especially proteins, its ions also form other compounds with a variety of soluble compounds and this allows for the formation of the skeleton [74].

Calcium is stored in bones and teeth by 99%, but it is also found in muscles, blood and intercellular fluids by 1%. The body accurately regulates the level of calcium in the blood and cells by two hormones (calcitonin and parathyroid hormone) in order to perform daily vital functions [75].

The body obtains calcium either through foods and nutritional supplements that contain it, or by withdrawing calcium from the body (removing calcium from the bones). This process is called bone resorption by the Parathyroid hormone PTH, and it occurs when the body does not get enough calcium through food [76].

1.6.3. Phosphorus

Phosphorus is the second most abundant mineral in the body after calcium. It is found in both organic and inorganic forms. Organic compounds of phosphorus are toxic, so only the inorganic form is measured. Inorganic phosphorus performs an important function in the bones and teeth, as it supports the growth of the body structure and is involved in the synthesis of phosphate, which is one of the components of nucleotide derivatives (GTP, ATP, NADP). It also works to provide phosphate to the fluid inside and outside the cells [77].

Phosphates play a pivotal role in the structure of DNA and RNA molecules, which are essential acids for reproduction and protein synthesis; it is also involved in the synthesis of ATP, which is necessary for cellular energy transfer processes, for the important phosphorylation processes that occur within cells. Phosphates are also included in the composition of phospholipids, which are important components of cell membranes [78].

Phosphorus is mainly found in bones at a rate of (85) %, where it is transformed inside the body into calcium phosphate, which is important for the formation of bones and teeth. In cells, it is found at a rate of (14) %, and less than it in plasma by (1) % [79].

The body needs phosphorus on a daily basis to perform many important functions, including filtration of waste products, but it is higher than normal levels cause adverse effects on bone health; because the presence of excess amounts of it leads to the withdrawal of calcium from the bones and thus their Fragility [80,81].

1.6.4. Albumin

Albumin is one of the most important proteins present in the bloodstream. It has a globular shape that constitutes about (50-60) % of plasma proteins. Albumin is soluble in water. It has a high molecular weight of about (66.7) kilo Daltons, with a single polypeptide chain that includes (585) amino acids and (3) symmetric helical texture domains and (17) disulfide bridge.

Albumin is found in plasma with a half-life of about (14-20) days and works to transport proteins with a negative charge such as bilirubin, thyroxine and cortisol [82].

Albumin is a multifunctional protein and its biological functions are related to its molecular composition, distribution within the body, and complex structure. Its high concentration inside the vessels and its negative charge are the basis for its role as a major regulator of fluid volume within the vessels.

Albumin has an external structure that facilitates its physiological functions, which are represented in controlling the pH, osmotic pressure, and other functions, in addition to its work as an antioxidant, metabolite, nutrient, drug, and ion. It is also believed to have anti-inflammatory functions [83].

Albumin is manufactured in the liver which is its main factory and is released into the blood vessels to reach the tissues. The normal rate of albumin in the blood ranges between (5.3-5.5) grams per deciliter and its level in the blood may decrease or exceed normal as a result of several factors including liver failure, heart failure, and chronic renal failure, as poor kidney function leads to the excretion of large amounts of protein in the urine as a result of kidney damage [84].

1.6.5. Hemoglobin

Hemoglobin is a spherical, multi-unit metallic protein attached to a heme group, one of which contains an Iron molecule. Hemoglobin is found in red blood cells and occupies about (90) % of their dry weight and (34) % of their total content (Including water). Hemoglobin transports oxygen to all cells of the body and returns carbon dioxide from tissues and organs to the lungs [85].

Hemoglobin is found in all vertebrates except fish and in humans. It is present in more than one gene HBB, HBA1, HBA2. it has an important role in maintaining the blood pH at 7.4, in addition to serving as a buffer for the action of enzymes [86,87,88].

Hemoglobin maintains the normal shape of red blood cells, which are usually round or circular and contain a cavity in the middle of them. Hemoglobin also helps red blood cells move easily through blood vessels, so any problems that occur in its shape and proportion negatively affect the natural shape of red blood cells [89].

Hemoglobin consists of two main parts, heme, which is the organic compound that constitutes only (4) % of the weight of the molecule and resembles a ring attached to an Iron atom that is responsible for giving blood its red color (dye) and transporting oxygen and carbon dioxide. The second part is globing (protein) and there are four different molecules of protein (alpha, beta, delta, and Kama) and these molecules are folded chains consisting of the largest possible number of different amino acids called peptides carrying Iron molecules inside them and connected to each other forming a tetrahedral structure as show in the following figure [90].

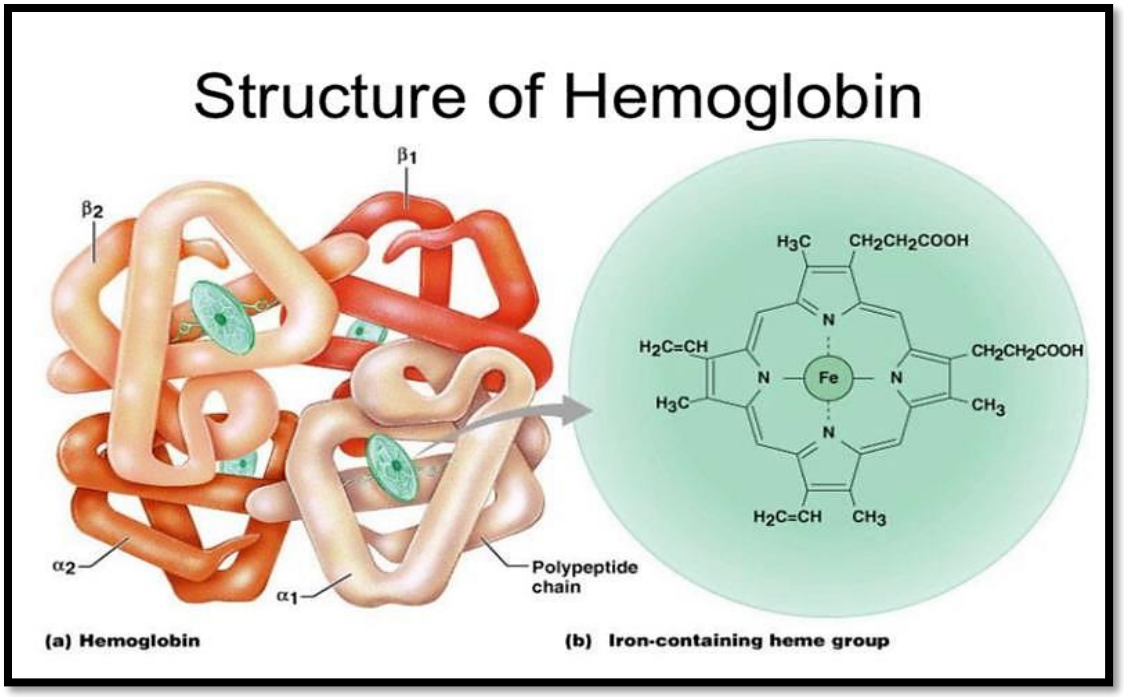

Fig. (1-9): Structure of Hemoglobin [91,92].

Hemoglobin also binds to other bonds, including (sulfide, nitrogen oxide, and cyanide) and transports drugs to their sites of action.

Hemoglobin forms an unstable, reversible bond when it carries oxygen. It is called oxidized hemoglobin (oxyhemoglobin) and its color is dark red. In the event that it is not saturated with oxygen molecules, it is called (deoxyhemoglobin) which is not oxidized and its color is blue-purple. It is the reduced state of hemoglobin in which it is a carrier of carbon monoxide [93].

Hemoglobin develops in the bone marrow cells which become red blood cells after (120) days which is the period at which the life of the red blood cells ends. so, the hemoglobin breaks down and comes out of these cells, as for iron, it is transferred from hemoglobin to the bone marrow by proteins called transferring, where it is used again to produce new red blood cells, and the remaining hemoglobin forms bilirubin, a chemical that is secreted in bile and then into the intestine to help in the digestion process [94].

Hemoglobin is also found outside red blood cells, such as liver cells, macrophages, and menial cells in the kidneys in the pigment epithelium, and in the retina. Its role is an antioxidant, a regulator of Iron metabolism, and a non-carrier of oxygen [95,96].

Normal hemoglobin in the body varies from person to person at first, depending on age, but it depends on gender, starting from adolescence, so men have higher rates of it compared to women [97].

1.6.6. Creatine Kinase

It is also known as creatine phospho-kinase which is an enzyme protein that belongs to a large family of kinases with a high molecular weight of about (80) kilo Daltons. The enzyme creatine kinase is important for energy metabolism, especially in cells that consume high energy, such as muscles. The enzyme is found primarily in skeletal muscle nerve and smooth cells, and in the heart muscle and brain.

Creatine kinase enzyme consists of two different subunits M (muscle type) and B (brain type) and has three active isoforms that can be distinguished by electrophoresis.

CK-MM is found in skeletal muscles and occupies about (95%) of the total weight, CK-MB is found specifically in the heart muscle and occupies only (5%) while CK-BB is found in the brain, and there is another additional form that is found in the mitochondria and is one of Type CK-Mt [98].

The main function of the enzyme is to catalyze the reverse phosphorylation of creatine (the conversion of creatine into phosphocreatine) by ATP and the generation of ADP and the reverse reaction.

The distribution of the enzyme varies between the tissues of the body, as it is found abundantly in parts that need high energy, such as muscles, and it is found at normal levels in the body. However, and the values for women are about half of the values for men in some cases. Thus, its levels may rise above the normal limit in the body due to several conditions, such as rhabdomyolysis, or as a result of strenuous exercise, acute myocardial infarction and chronic renal failure [99,100,101].

Also, enzyme levels are high in newborns, up to ten times the normal rate due to the physiological stress of childbirth and remain high for a period of (6-10) weeks [102].

1.7. The Aims of the Study

1. To know the effect of carnitine treatment on hemodialysis patients.
2. Evaluation of some electrolytes such as calcium and phosphorus on hemodialysis patients.
3. To know the effect of L-carnitine on the levels of PTH hormone and CPK enzyme, Hb, Albumin, Ca, PO4 in patients of chronic renal failure.

CHAPTER TWO

MATERIALS AND METHODS

2.1 Materials

2.1.1 Chemical and Kits .

All laboratory chemicals used as supplied, further purifying chemicals and kits, used in this work are listed in table (2-1)

Table. (2-1): Chemicals and kits.

Chemicals / Kit	Source
Parathyroid Hormone Kit	Roche -Switzerland (Japan)
Phosphorus Determination Kit	Spin Reacts (Spain)
Calcium Determination Kit	Egyptian Company for Biotechnology (S. A. E) (Egypt)
Albumin Determination Kit	Biolab SAS (France)
Creatine Kinase Enzyme Determination Kit	Costa Brava Barcelona (Spain)

2.1.2-Apparatus Analysis and Equipment

The apparatus and equipment used in this work are listed in table (2-2)

Table. (2-2): The apparatus and equipment.

Instruments and Tools	Suppliers
Centrifuge	Heraeus (Germany)
Micropipette 10-1000ul	Slamed (Germany)
Mindray CL - 1000i	Shenzhen, Guangdong, (China)
CBC CellTac MEK -6510	Japan
Fujifilm DRl – CHem NX500	Japan
Spectrophotometer type 21	Miltion Roy (Switzerland)
EDTA tube	Plastilab (China)
Eppendorf tubes (diversified Size) (0.2,0.5,1.5) ml	China
Ur 1800 UV -Visible Spectrophotometer	Shimadzu (Germany)
Gel tube	China
Human star 300 SR	French
Shaker	Jencons (scientific) England
Water Bath	Slamed (Germany)

2.1.3 Subjects and study design

A case-control study has been conducted at Imam Al-Sadiq Teaching Hospital in Babli Governorate, Division of the Industrial College (dialysis). All samples were collected from August 2022 to March 2023. This study included 40 patients (25) males and (15) females, aged between (62- 21) years old, and the patients were distributed over different periods of time, suffering from chronic kidney disease and undergoing renal dialysis, from three months to a year. The majority of patients were suffering from kidney stones, diabetes and irregular blood pressure. The study was divided into two phases, the pre-treatment phase and the second phase, three months after the treatment. The treatment was distributed to the patients in an oral form (capsule) at a dose of (1600) mg per day. All dialysis patients underwent a physical examination and a brief questionnaire, including the patient s age, sex, disease duration, weight, height, number of dialysis times per week, and other diseases. (Chronic or hereditary), all patient information was stored in computerized systems in the SPSS program. The clinical outline of the study is presented in the table (2-3).

Table (2-3): Questionnaire of this study

Patient Profile				
Name:	Age:	Sex:	Weight:	Length:
Duration:	Number of Washes:	Other disease:		
Measured Parameters				
PTH Ca PO4	Albumin	Hemoglobin	CK enzyme	

2.1.4- Stages of this study

In two study stages, this was confirmed:

1. The pre-treatment stage includes all (40) patients in the study, whose ages range from (21-62).
2. The post-treatment stage, which includes all (40) patients in the study, whose ages range from (21-62).

2.1.5- Exclusion Criteria

Patients with hypothyroidism, blood allergies, and neurological seizures (epilepsy) were excluded. Children, pregnant women, and infants were also excluded.

2.1.6– Collect Blood Sample

Blood samples were taken from dialysis patients at Imam Al-Sadiq Teaching Hospital, Industrial College Division (dialysis) for the purpose of conducting the required medical examinations for patients. Five ml of blood was taken using a 5ml medical syringe and the blood was placed in gelatine tubes (gel tube) free of anti-clotting material, as it contains a gelatinous substance that helps to increase the separation of serum formed after the centrifugation process. The samples were left for 15 minutes at room temperature, after which they were inside a centrifuged at a speed of 2500 (round /minute) for 10 minutes to obtain the serum that was stored at (-20) °C, unless it was used immediately.

2.2- Methods: -

2.2.1- Measurement of Body Mass Index: -

Body mass index were calculated from the following equation [103].

BMI = Weight (kg)/Height (m2)

They were classified into four groups:

1. The BMI of underweight range is ($<$ 18.5) Kg/m^2
2. The BMI of normal range is (18.5-24.9) Kg/m^2
3. The BMI of overweight range is (25-29.9) Kg/m^2
4. The BMI of obese range is ($>$ 30) Kg/m^2

2.2.2 - Determination of Parathyroid Hormone Levels

PTH level was measured by Coba's immunoassay analyzer utilizing the electrochemiluminescence immunoassay (ECLIA), the using kit supplied by Roche – Switzerland. The principle of test is sandwich principle where the duration of assay is 18 minutes that involve two incubation period through

which the N- terminal fragment was reacted biotinylated monoclonal antibody while the C- terminal was reacted ruthenium labeled antibody. The antibodies used in this analysis were reactive with epitopes in the amino acid regions.

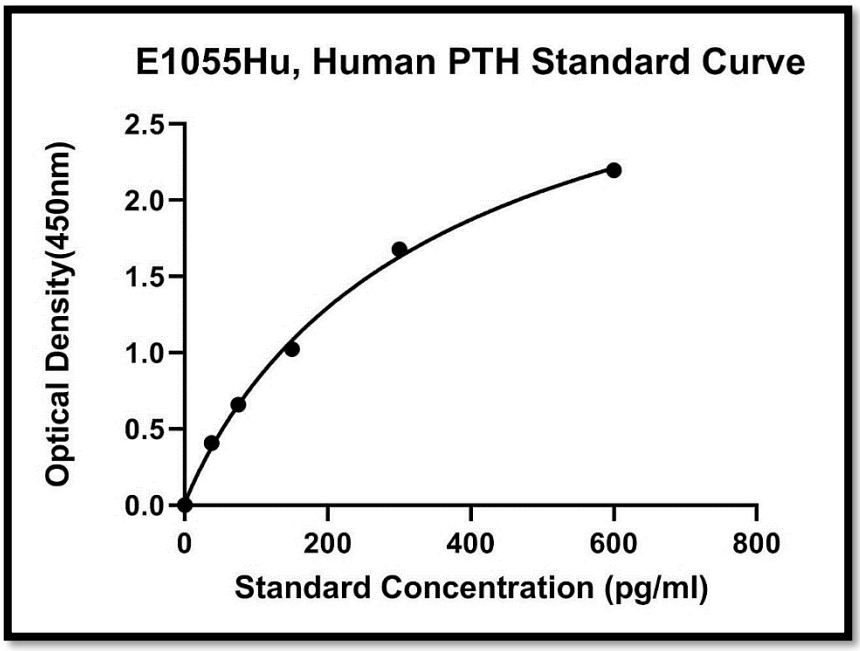

Fig. (2-1): Standard Curve of Determination of (PTH) Concentration

2.2.3- Determination of Total Serum Calcium Concentration

Method: -

The method is O-cresol phthalein complex one colorimetric method.

Principle: -

In an alkaline environment a complex created which has a violet color, resulting from the reaction of O-cresol phthalein complex one (O-CPC) with the ions of calcium [104].

Alkaline pH

O-CPC + Ca^{+2} complex of calcium-O-CPC

The strength of color of the resulting complex proportionate to the concentration of calcium.

i. Reagents: -

1. Calcium standard: Calcium (10 mg/100 mL), or (2.5 mmol/L).
2. R1: Reagent 1 (buffer) was the chemical substance (2-amino-2-methyl-propanol) at (10.5) pH, 0.3 mmol/L.
3. R2: Reagent 2 the (chromogen) encompassed the compound (O-cresol phthalein complex one 0.16 mmol/L), and (8-hydroxyquinoline 7 mmol/L).

ii.Test Procedure: -

Three sets of test tubes were created, and reagents and samples were added to them as needed, shown in table (2-4).

Table (2-4): Procedure for Determination of Total Serum Calcium.

Tubes	Blank	Standard	Sample
Sample			**10 µl**
Standard		**10 µl**	
Reagent 2	**0.5 ml**	**0.5ml**	**0.5 ml**
Reagent 1	**0.5ml**	**0.5ml**	**0.5 ml**
Blending was done to the contents of the tubes. The tubes were incubated at 20-25°C for a period of 5 minutes. At 587 nm, the absorbances were measured against blank.			

iii. Calculations: -

Concentration of calcium = A specimen / A standard × standard concentration.

As stated by the equation below, corrected total calcium was gained [105].

Concentration of corrected total calcium in mmol/L =

[(40 – albumin in g/L) ×0.02] + measured total calcium in mmol/L.

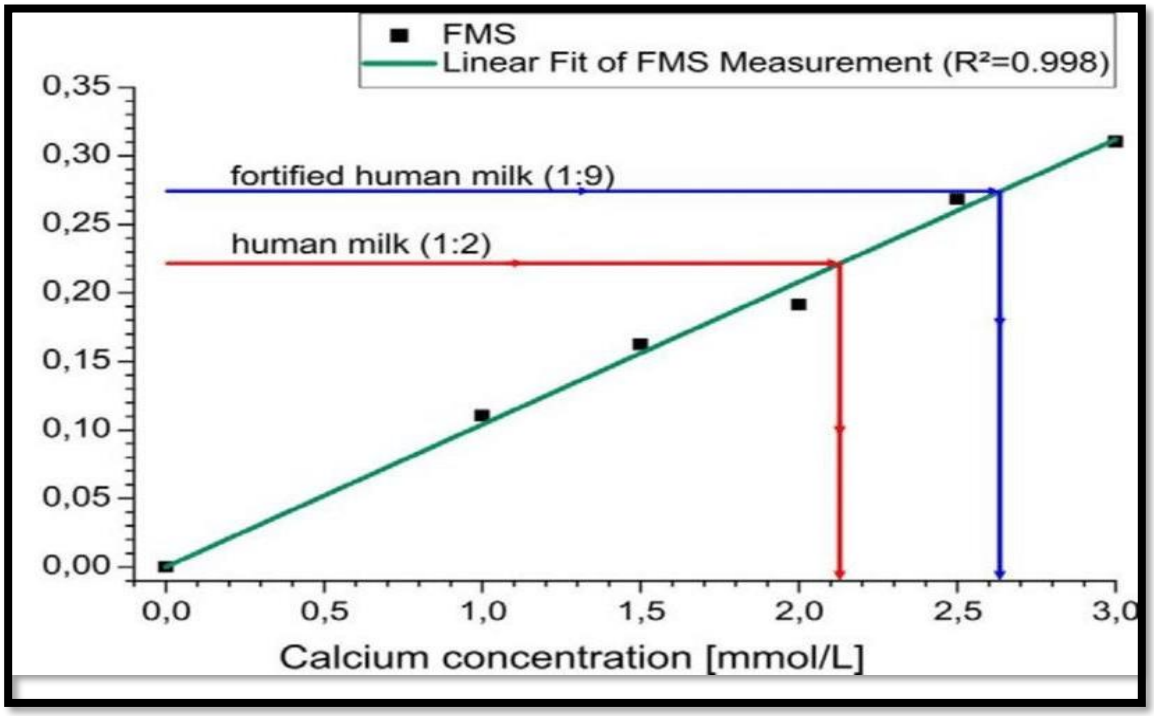

Fig. (2-2): Standard Curve of Determination of (Ca) Concentration

2.2.4- Determination of Serum Phosphorus Concentration

Principle: -

The complex (phosphomolybdic) created when the reaction between molybdic acid and inorganic phosphorus happens. When complex reduction subsequently occurs in alkaline environment a blue molybdenum color generated. The color strength commensurate to the concentration of inorganic phosphorus in the test specimen [106].

i. Reagents compositions: -

R1 Molybdic: It composed of molybdate-borate (1.21 mmol/L) and sulphuric acid (100 mmol/L).

R2 (Catalyzer): 1,2 Phenylenediamine (2,59 mmol/L).

Phosphorus CAL: Aqueous primary phosphorus standard (5 mg/dL).
Conversion factor: mg/dL × 0.323 = mmol/L.

ii. Method: -

Via combining similar volumes of (Molybdic) with (Catalyzer)

The working reagent was made. Then, three sets of Identified test tubes were produced, and reagent and sample quantities were added to them as needed, shown in table (2-5).

Table. (2-5): Procedure for Determination of Serum Phosphorous

Tubes	**Blank**	**Standard**	**Sample**
Standard		**50 µl**	
Sample			**50 µl**
The Working reagent	**1.5 ml**	**1.5 ml**	**1.5ml**
The substances Inside the tube were fully blended. Posteriorly, on 37°C lasting ten minutes, all tubes were incubated. At 710 nm (620-750 nm), the absorbance values were recorded against the blank.			

iii. Calculations: -

Result = (A Sample – A Blank) / (A Standard – A Blank) × Standard concentration

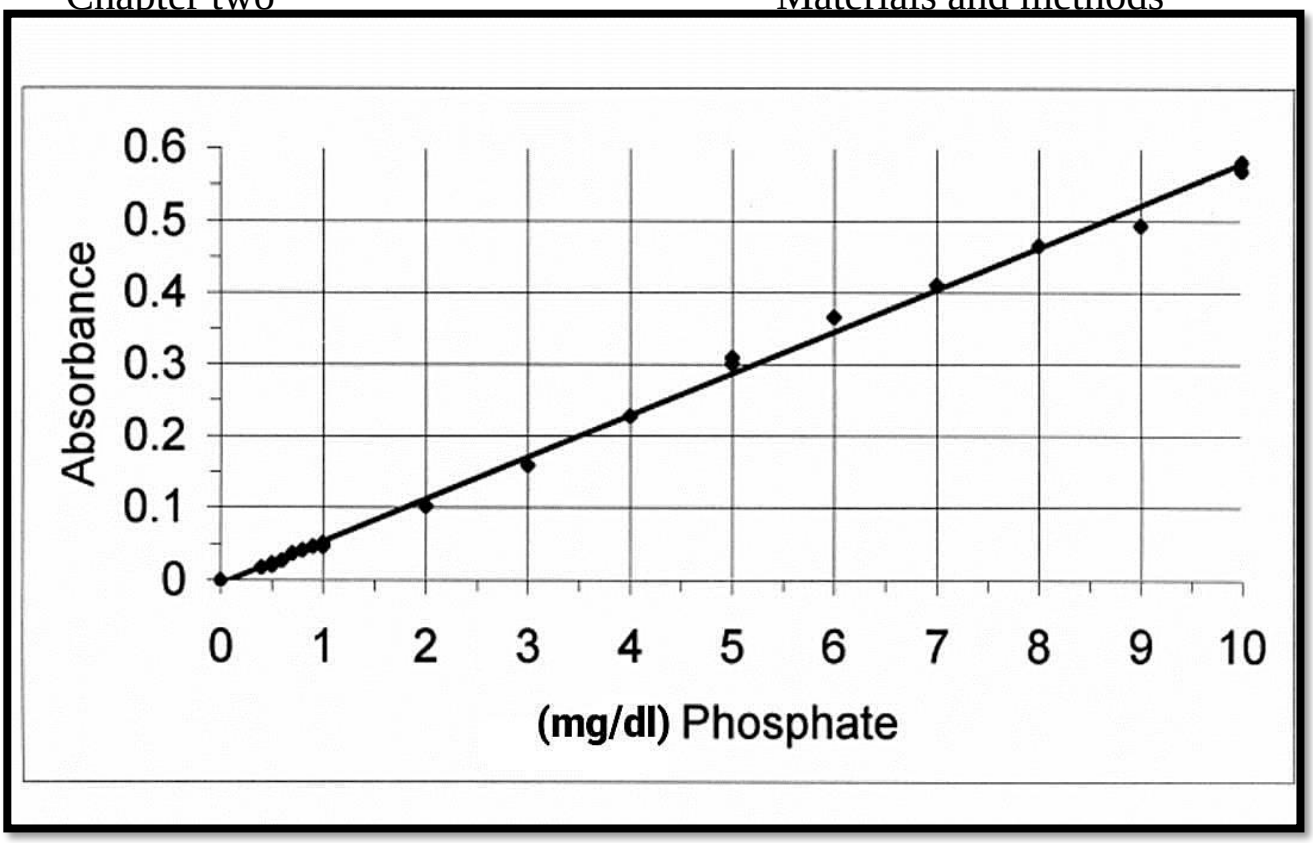

Fig. (2-3): Standard Curve of Determination of (PO4) Concentration

2.2.5- Determination of Serum Albumin Concentration

Principle: -

Bromocresol green Combines the Albumin to generate a Colorized Product in buffered Solution at (PH 4.2). At 630nm (620-640), the Colorized Product an absorbance is determined where it Commensurate to the amount of albumin exists in the test Sample [107].

i. Reagents: -

R1 Vial: -Bromocresol green reagent which included: -

-Succinic acid in Concentricity :(83mmol/L),

-Bromocresol green with concentration :(167µmol/L),

-Sodium hydroxideat concentration :(50mmol/L),

-Poly oxyethylene monolauryl ether with concentration :(1g/L).

R2 Vial: - Standard which was bovine albumin at concentration (5g/dL).

ii. Procedure: -

Three sets of test tubes were prepared, volumes of reagents, sample and demineralized water were added into them as appeared in table (2-6).

Table (2-6): Procedure for Determination of Serum Albumin.

Tubes	Blank	Standard	Sample
R1	**2ml**	**2ml**	**2ml**
Water (demineralized)	**10µl**		
Sample			**10µl**
R2		**10µl**	
The Contents of the tubes were well mixed. During a period of three minutes, at 630nm (620-640), the absorbances were delivered against blank.			

iii. Calculation: -

Albumin Concentration = (A sample /A standard) × standard concentration.

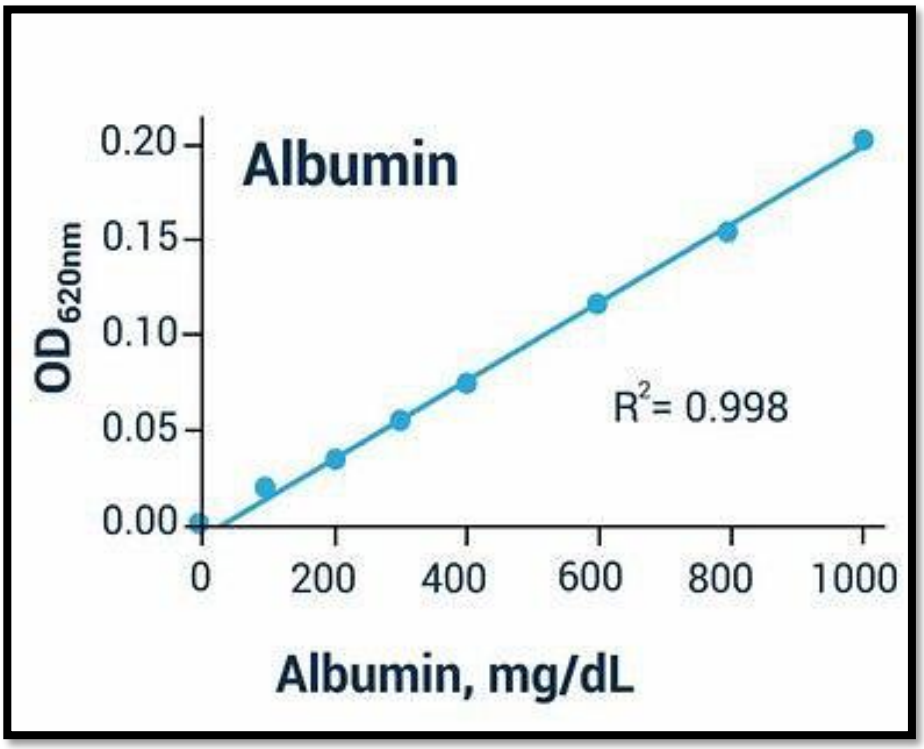

Fig. (2-4): Standard Curve of Determination of Albumin Concentration

2.2.6- Determination of Hemoglobin Concentration

The hemoglobin concentration was measured with a comprehensive blood test device CBC Cell Tac, a sufficient amount of the patient s blood was withdrawn, not exceeding 2ml, and placed in an EDTA tube containing anticoagulant to preserve the blood components in full. Then the tube was placed on the shaker for ten minutes for the purpose of mixing the sample and disposing of it the blood clot, after recording the patient's information in the device, the tube containing the blood was placed in the needle of the CBC device and within 15 minutes the results appeared.

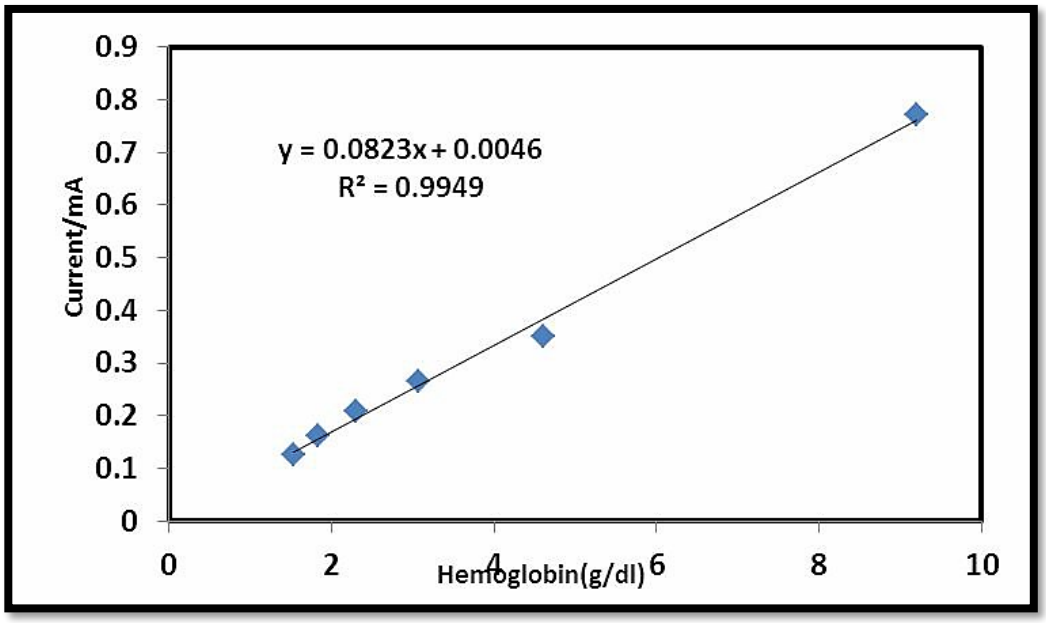

Fig. (2-5): Standard Curve of Determination of (Hb) Concentration

2.2.7- Determination of Total Serum Creatine kinase CK Enzyme Concentration

Assay Principle

Creatine kinase (CK) catalyzes ADP phosphorylation via creatine phosphate, and creatine obtains ATP. The catalytic concentration was determined, using the hexokinases and glucose-6-phosphate dehydrogenase reactions, from the measured average of NADPH at 340 nm.

$$\text{Creatine phosphate} + \text{ADP} \xrightarrow{CK} \text{Creatine} + \text{ATP}$$

$$\text{ATP} + \text{Glucose} \xrightarrow{HK} \text{ADP} + \text{Glucose-6-phosphate}$$

$$\text{Glucose-6-phosphate} + \text{NADP}^+ \xrightarrow{G6PDH} \text{6-Phosphogluconate} + \text{NADPH} + \text{H}^+$$

i.Reagents: -

R1 include: - lamidazol 125mmol/L, EDTA 2mmol/L, magnesium acetate 12.5mmol /L, D-glucose 25mmol /L, N-acetyl cysteine 25mmol /L, hexokinase 6000U/L, NADP 2.4mmol/L, PH 6.7.

R2 include: - Creatine phosphate 250mmol/L, ADP 15mmol/L, AMP 25mmol/L, P1 -P5 Di (adenosine-5-) Penta Phosphate 102 µmol/L, glucose -6- phosphate dehydrogenase 8000 U/L.

ii.Test Procedure

Prepare the reaction solution first by adding (5 volume) of R1 to (1 volume) of R2

R1 (5 volume) +R2 (1 volume)

Table (2-7): Procedure for Determination of Serum CPK enzyme.

Working Reagent	**1ml**
Serum	**50µl**
Mix and read Kinetic assay.	

iii.Calculation

The CK concentration in the sample is calculated using the following general formula [108].

$$\Delta A/min \times Vt \times 10^6 / Ɛ \times 1 \times Vs = U/L$$

1. ΔA/min: Readings difference/minute
2. Ɛ: The molar absorbance coefficient for NADPH at 340 nm is 6300
3. 1: The light path is 1 cm
4. Vt : The total reaction volume is 1.05
5. Vs : The sample size is 0.05
6. 1 U/L = 16.6 nkat / L

ΔA/min	**× 3333 = CK (U/L)** **× 55561 = CK (nkat/L)**

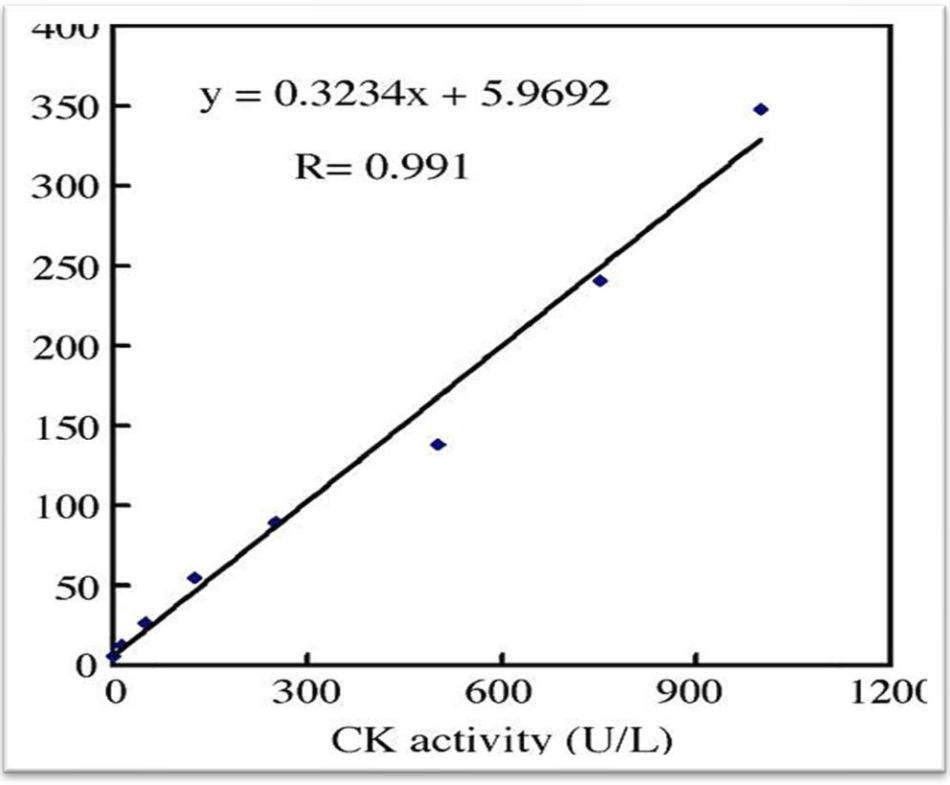

Fig. (2-6): Standard Curve of Determination of (CK) Concentration

2.2.8- Data Analysis

Statistical analysis was carried by-using SPSS version 27. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Paired t-test was used to compare means for two paired readings. McNemar test was used to compare paired categorical variables. A p-value of ≤ 0.05 was considered as significant.

CHAPTER THREE

THE RESULTS

3.1 Distribution of Patients According to the Gender

Show the distribution of patients with hemodialysis according to socio-demographic characteristics including (age and gender). Mean age of patients was (36.93 ± 10.99) with older patient was 62 years and younger patient was 21 years. Majority of patients (N=25, 62.5%) were males.

Table 3.1: Distribution of Patients According to the Gender

Study variables	**(Mean± SD)**	**Minimum- Maximum**
Age (years)	(36.93 ± 10.99)	(21-62)
Gender	**Number**	**%**
Male	25	62.5%
Female	15	37.5%
Total	40	100.0%

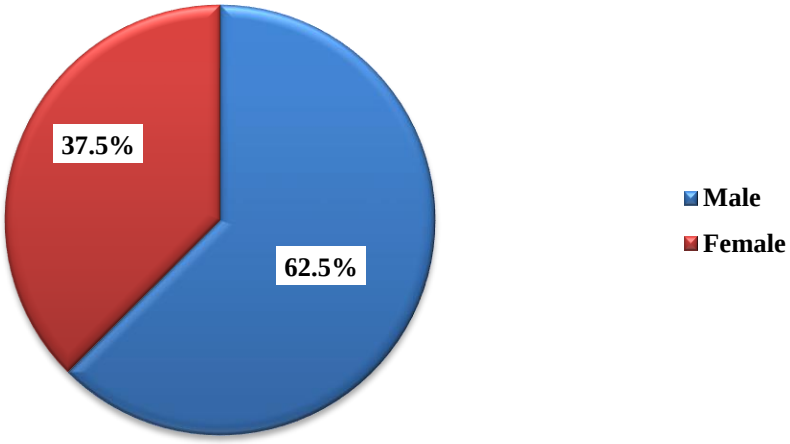

Figure 3.1: Distribution of Patients According to the Gender

3.2: The Mean Differences of Parathyroid Hormone Before and After Treatment

There were significant mean reduction of Parathyroid hormone after 3 months treatment with L-carnitine among patients on hemodialysis.

Table 3.2: The Mean Differences of Parathyroid Hormone Before and After Treatment

Study variable	Periods of assessment	N	Mean ± SD	P-value
Parathyroid hormone (pg /ml)	Before treatment	40	360.60 ± 258.37	**<0.001***
	After treatment	40	208.68 ± 190.77	

*P value ≤ 0.05 was significant.

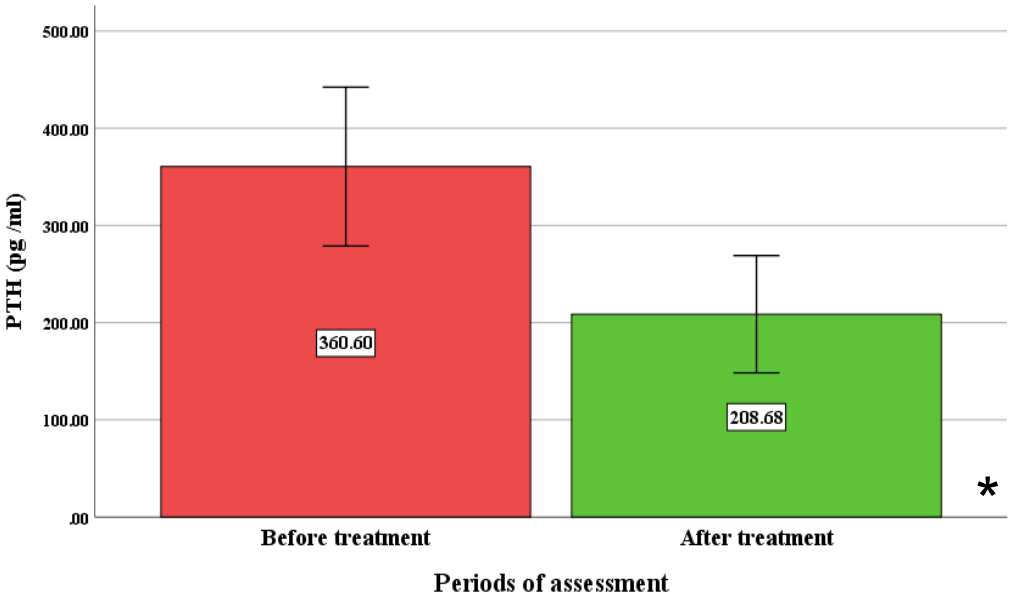

Figure 3.2: The Mean Differences of Parathyroid Hormone Before and After Treatment

3.3: The Mean Differences of Calcium Before and After Treatment

There were significant mean elevation of Calcium (mmol /l) after 3 months treatment with L-carnitine among patients on hemodialysis.

Table 3.3: The Mean Differences of Calcium Before and After Treatment

Study variable	Periods of assessment	N	Mean ± SD	P-value
Calcium (mmol /l)	Before treatment	40	1.12 ± 0.39	**<0.001***
	After treatment	40	2.38 ± 0.33	

*P value ≤ 0.05 was significant.

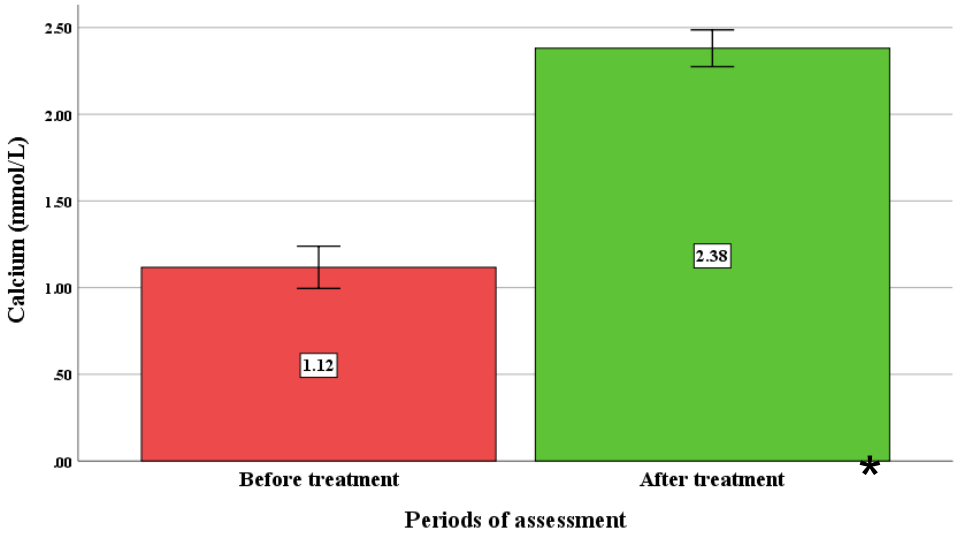

Figure 3.3: The Mean Differences of Calcium Before and After Treatment

3.4: The Mean Differences of Phosphorus Before and After Treatment

There were significant mean reduction of Phosphorus (mg /dl) after 3 months treatment with L-carnitine among patients on hemodialysis.

Table 3.4: The Mean Differences of Phosphorus Before and After Treatment

Study variable	Periods of assessment	N	Mean ± SD	P-value
Phosphorus (mg /dl)	Before treatment	40	6.35 ± 2.49	**<0.001***
	After treatment	40	3.82 ± 1.44	

*P value ≤ 0.05 was significant.

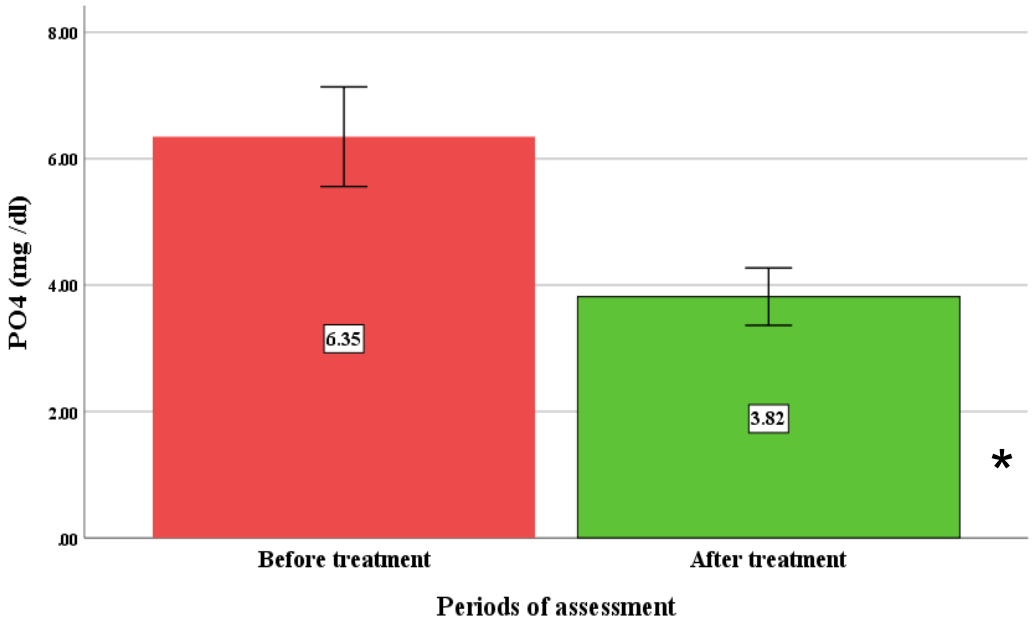

Figure 3.4: The Mean Differences of Phosphorus Before and After Treatment

3.5: The Mean Differences of Albumin Before and After Treatment

There were significant mean elevation of Albumin (mg /dl) after 3 months treatment with L-carnitine among patients on hemodialysis.

Table 3.5: The Mean Differences of Albumin Before and After Treatment

Study variable	Periods of assessment	N	Mean ± SD	P-value
Albumin (mg /dl)	Before treatment	40	3.05 ± 0.58	**<0.001***
	After treatment	40	4.44 ± 0.60	

*P value ≤ 0.05 was significant.

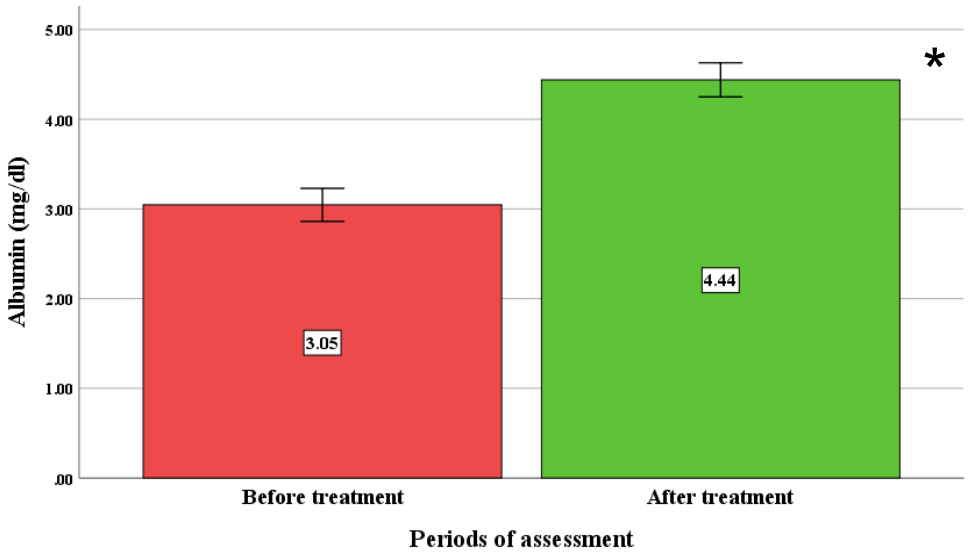

Figure 3.5: The Mean Differences of Albumin Before and After Treatment

3.6: The Mean Differences of Hemoglobin Before and After Treatment

There were significant mean elevation of Hemoglobin (g /dl) after 3 months treatment with L-carnitine among patients on hemodialysis.

Table 3.6: The Mean Differences of Hemoglobin Before and After Treatment

Study variable	Periods of assessment	N	Mean ± SD	P-value
Hemoglobin (g /dl)	Before treatment	40	9.21 ± 1.30	**<0.001***
	After treatment	40	13.58 ± 1.08	

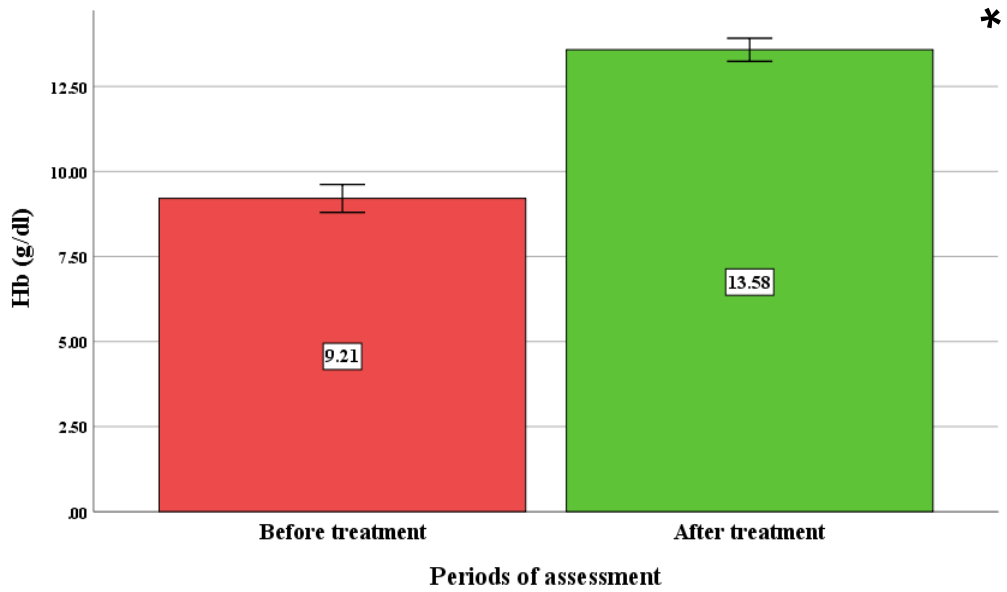

Figure 3.6: The Mean Differences of Hemoglobin Before and After Treatment

3.7: The Mean Differences of Creatine Kinase Before and After Treatment

There were significant mean reduction of Creatine kinase (U/l) after 3 months treatment with L-carnitine among patients on hemodialysis.

Table 3.7: The Mean Differences of Creatine Kinase Before and After Treatment

Study variable	Periods of assessment	N	Mean ± SD	P-value
Creatine kinase (U/l)	Before treatment	40	280.41 ± 199.47	**<0.001***
	After treatment	40	109.01 ± 80.50	

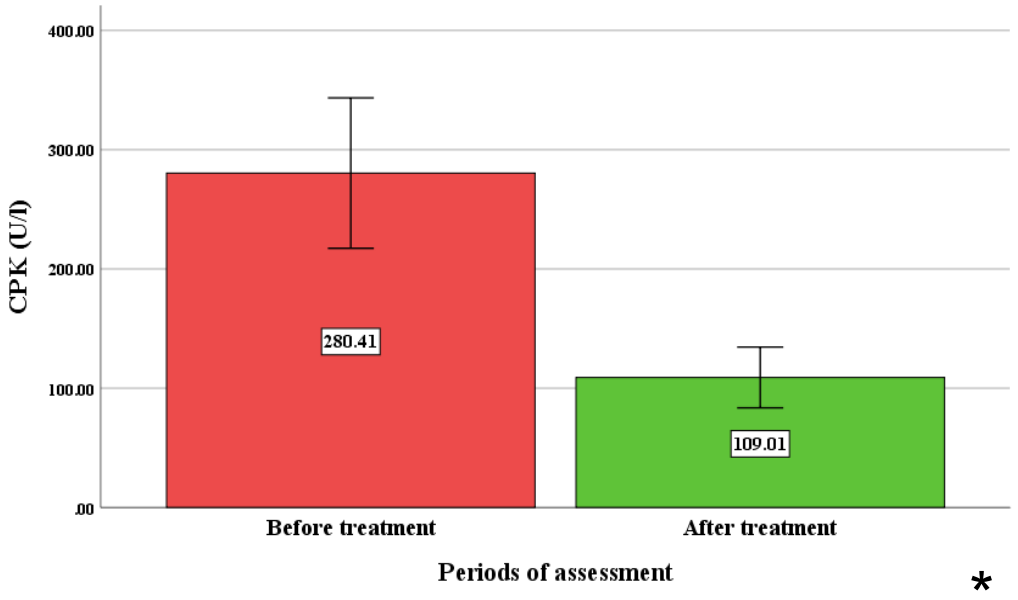

Figure 3.7: The Mean Differences of Creatine Kinase Before and After Treatment

3.8: Distribution of Patients with Hemodialysis According to Body Mass Index

including underweight (<18.5), normal (18.5-24.9), overweight (25-29.9) and obese (≥ 30) before and after 3 months treatment with L-carnitine.

Table 3.8 Distribution of Patients with Hemodialysis According to Body Mass Index

Body mass index (kg/m^2)	Periods of assessment	
	Before treatment	After treatment
Underweight (<18.5)	2 (5.0)	1 (2.5)
Normal (18.5-24.9)	22 (55.0)	24 (60.0)
Overweight (25-29.9)	9 (22.5)	12 (30.0)
Obese (≥ 30)	7 (17.5)	3 (7.5)
Total	40 (100.0)	40 (100.0)

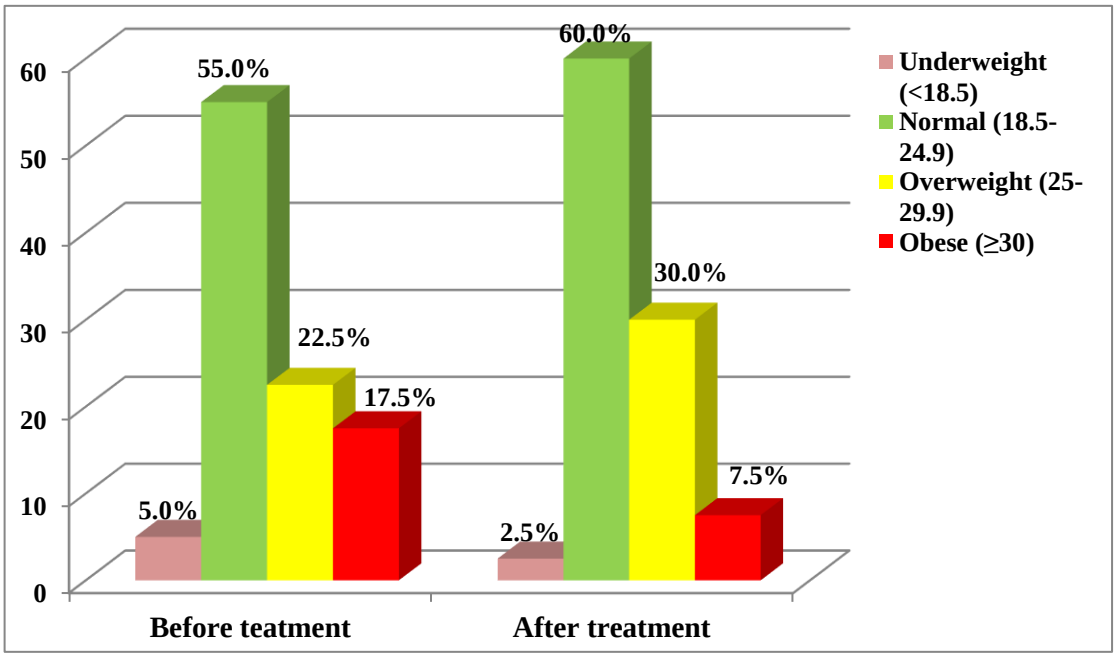

Figure 3.8: Distribution of Patients with Hemodialysis According to Body Mass Index

3.9: The Mean Differences of Body Mass Index Before and After Treatment

There were no significant mean differences of body mass index (kg/m^2) before and after 3 months treatment with L-carnitine among patients on hemodialysis.

Table 3.9: The Mean Differences of Body Mass Index Before and After Treatment

Study variable	Periods of assessment	N	Mean ± SD	P-value
BMI (kg/m^2)	Before treatment	40	24.93 ± 5.14	0.197
	After treatment	40	24.55 ± 3.63	

*P value ≤ 0.05 was significant.

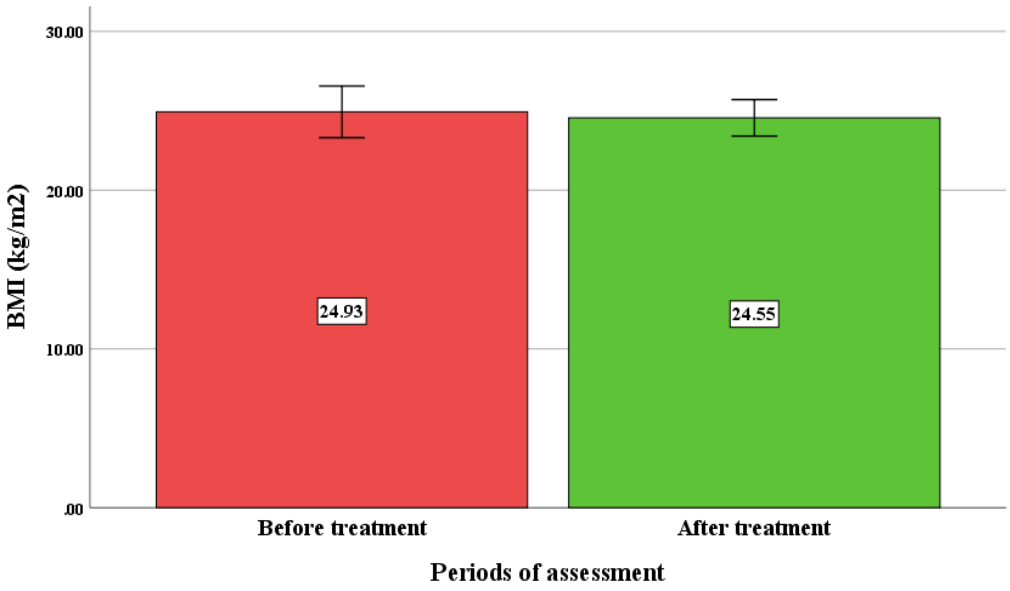

Figure 3.9: The Mean Differences of Body Mass Index Before and After Treatment

3.10: Distribution of Patients According to the Number of Washing Times Per Week

including (once per week, twice per week and 3 times per week) before and after 3 months treatment with L-carnitine.

Table 3.10 Distribution of Patients According to the Number of Washing Times Per Week

Number of hemodialysis per week	Periods of assessment	
	Before treatment	After treatment
Once per week	5 (12.5)	14 (35.0)
Twice per week	19 (47.5)	19 (47.5)
3 times per week	16 (40.0)	7 (17.5)
Total	40 (100.0)	40 (100.0)

***P value ≤ 0.05 was significant. McNemar Test.**

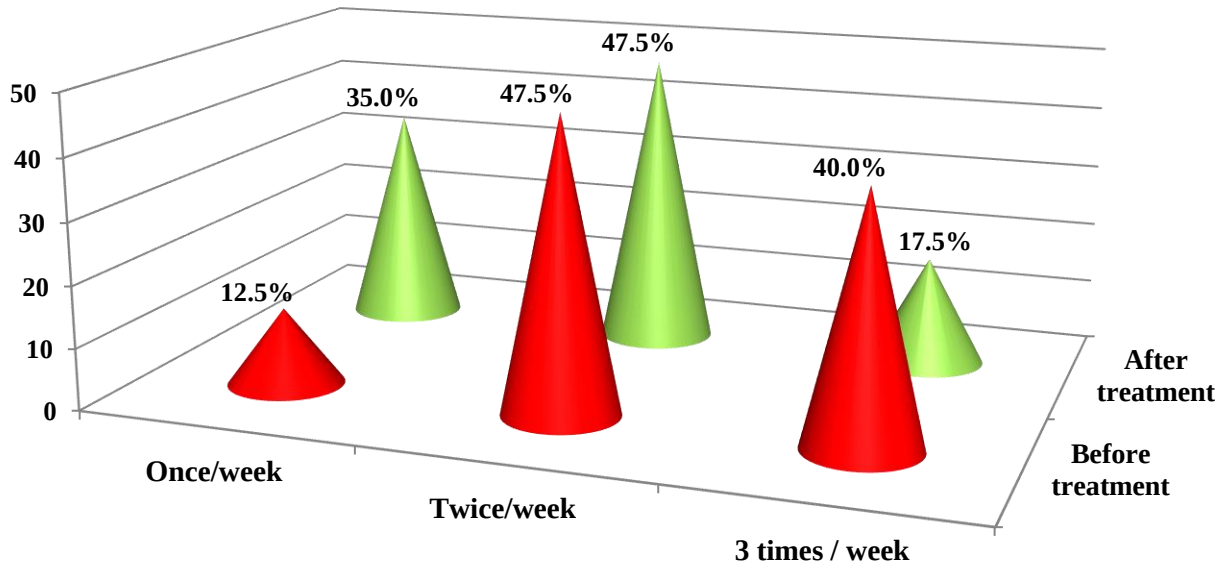

Figure 3.10: Distribution of Patients According to the Number of Washing Times Per Week

3.11: Shows Distribution of Patients with Hemodialysis According to Past Medical History

Shows distribution of patients with hemodialysis according to past medical history including (diabetes mellitus, hypertension and renal stone). More than half of patients (N=21, 52.5%) presented with history of diabetes mellitus. Hypertension was positive in majority of patients (N=34, 85.0%) and history of renal stone was positive in only eight patients (20.0%).

Table 3.11 Shows Distribution of Patients with Hemodialysis According to Past Medical History

Past medical history	Number	%
Diabetes mellitus		
Yes	21	52.5%
No	19	47.5%
Total	40	100.0%
Hypertension		
Yes	34	85.0%
No	6	15.0%
Total	40	100.0%
Renal stone		
Yes	8	20.0%
No	32	80.0%
Total	40	100.0%

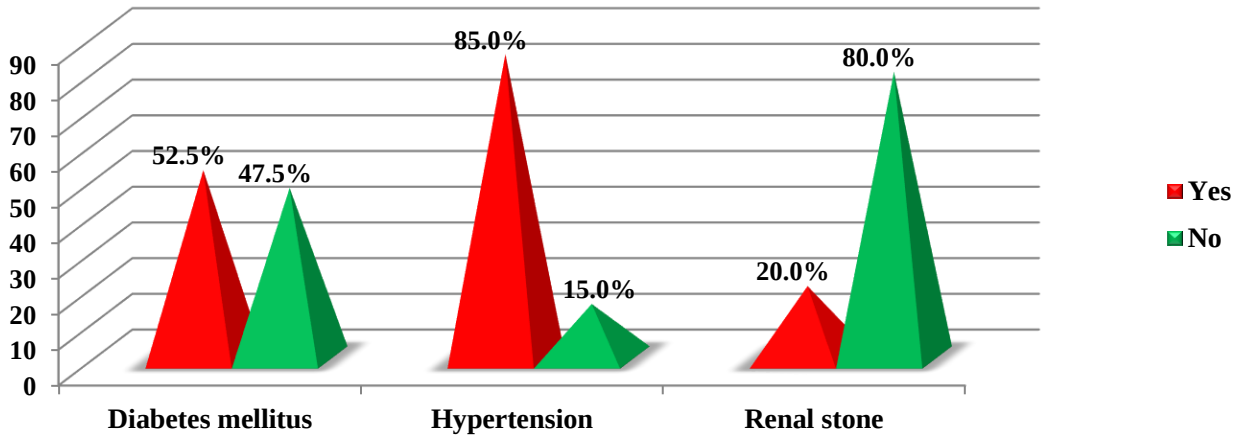

Figure 3.11: Distribution of Patients with Hemodialysis According to Past Medical History

CHAPTER FOUR

DISCUSSION

4.1. Effect of L-Carnitine Treatment on Vital Parameters Levels in Chronic Kidney Disease Patients Undergoing Hemodialysis.

Patients with chronic renal failure suffer from an increase in hospitalization and need dialysis due to the loss of kidney function [109].

They are more likely to suffer from low levels of carnitine which is one of the factors responsible for the various disorders that chronic kidney disease patients suffer from, such as anemia, muscle weakness, low pressure during dialysis, and cardiomyopathy, Maintaining the level of carnitine in the serum or tissues can reduce these disorders [110,111].

Secondary hyperparathyroidism and enlarged parathyroid glands are common complications in patients with renal failure due to the inability of the affected kidney to produce 1-alpha hydroxylase and the inability of the patient to convert vitamin D to its active form [112].

Decreased calcitriol in the blood, moderate decrease in ionized calcium, inability of the kidneys to excrete phosphate, and its rise in the blood contribute to the Increase in the synthesis and secretion of PTH hormone with the progression of the disease.

The increase in the level of PTH is associated with the occurrence of hyperparathyroidism in hemodialysis patients which is a physiological disease caused mainly by hyperphosphatemia and hypocalcemia [113].

In a study by Roman and Jaroslav et al. [114], L-Carnitine supplementation was used to investigate its effect on secondary hyperparathyroidism in hemodialysis patients and found that L-Carnitine had little effect and non-significant expression in patients with secondary PTH hyperactivity and this is inconsistent with the results of the current study.

Where the results of the current study showed a significant decrease ($P = 0.001$) In parathyroid hormone levels in dialysis patients who suffer from hyperactivity of PTH after three months of using L-Carnitine treatment compared to what they were before using the treatment as shown in figure [3-2].

Pre-treatment, patients with elevated PTH levels had hyperparathyroidism and elevated serum phosphorus levels [115] which is believed to be caused by an increase in the secretion of bone cells and not due to a decrease in kidney filtering [116]. Also, most of the dialysis patients were suffering from calcium deficiency due to irregular metabolism, as hyperparathyroidism stimulates the bone to release bone from the calcium in the blood [117]. Therefore, most patients suffer from bone pain and osteoporosis.

The most striking finding in this study was a decrease in phosphorus concentration and an increase in serum calcium concentration in hemodialysis patients treated with L-Carnitine, as shown in the two figures [3-3], [3-4].

The results of this study are consistent with the results of the study conducted by Ahmed et al. [118], Which explained the decrease in serum phosphorus concentrations in patients who received L-Carnitine treatment in three mechanisms:1/Improvement in residual renal function or dialysis efficiency,2/decrease in muscle mass or protein Intake,3/decrease in lean muscle catabolism and protein [119,120,121].

The results of this study showed a significant increase (P = 0.001) in the albumin level in patients who were treated with carnitine when compared to the same group of patients before treatment as shown in the figure [3-5].

Low albumin in hemodialysis patients is associated with malnutrition and inflammation [122]. It is one of the most common complications after malnutrition and is an independent risk factor for cardiovascular disease [123].

The results of the current study confirm those of another study by Rathod and Emami Naini et al., [124, 125], they found that L-Carnitine led to a greater increase in serum albumin and a greater decrease in creatinine in the blood. Therefore, it is recommended to follow L-Carnitine supplementation for all dialysis patients.

Another study data by Argani et al., indicated that oral administration of L-Carnitine to 40 patients for 2 months Increased plasma albumin levels, which is consistent with the results of our current study [126,127].

The results of the current study revealed a significant increase in hemoglobin levels in the group of patients treated with carnitine compared with the same group of patients before treatment, as shown in the figure [3-6].

This significant increase in hemoglobin levels in hemodialysis patients after three months of using the treatment is due to the beneficial effect of L-Carnitine on renal anemia, as L-Carnitine has been shown to reduce the erythropoietin dose requirement [128]. This result clearly indicates that L-carnitine has an important role in stabilizing the erythrocyte membrane, especially in patients with HD. which was consistent with the results shown by many studies [129].

In a study by Kitamura and Trovato et al., [130, 131], L-Carnitine has been shown to stimulate erythropoiesis [132,133].

The proposed mechanism for the beneficial effect of L-carnitine is to modulate lipid formation and to intensify the Na-K pump function in erythrocyte membranes, ultimately leading to an increase in the erythrocyte half-life, it also hypothesized an effect on erythroid precursors [134].

The results of this study revealed that oral administration of L-Carnitine increased Hb level over three months.

Sabry failed to identify any changes in hemoglobin levels after oral L-Carnitine administration over six months in hemodialysis patients [135].

Similar to the results of the previous study, our results confirmed the benefits of oral L-Carnitine on Hb levels In HD patients.

Heart failure and some of its complications, such as pulmonary edema, are a serious condition that dialysis patients suffer from. In the United States, the Kidney Data System revealed that an estimated 44% of HD patients suffer from cardiovascular disease, and about 5.4% of patients die from it [136], cardiovascular disease is associated with Impairment in daily living activities and quality of life in hemodialysis patients [137].

The Japan Society for Renal TransplantatIon and Dialysis reports that heart disease is the most common cause of death in HD patients [138].

It has recently been shown that L-Carnitine improves heart function in hemodialysis patients, as it is a natural substance that plays an important role in energy production and fatty acid oxidation in the mitochondria [139], Carnitine deficiency and dysfunction of enzymes in the outer and inner membranes of mitochondria leads to the inability to produce energy from long-chain fatty acids, which leads to the development of cardiomyopathy [140,141].

Serum L-carnitine levels in patients with HD decrease significantly as a result of serum L-carnitine being eliminated from the blood by HD [142,143].

In this study, it was observed that dialysis patients had a low concentration of free carnitine in the blood and a high concentration of CPK enzyme. After three months of treatment with carnitine, it is noticed that the plasma carnitine concentration was approximately ten times higher in dialysis patients who were treated with oral L-Carnitine after each dialysis session compared to what they were before receiving treatment and there was a significant decrease in the values of the enzyme creatine phospho kinase ($P = 0.001$) and an improvement in blood circulation, as shown in the figure [3-7].

A study by Miki Sugiyama and Takuma Hazama et al. [144], That illustrated L-Carnitine supplementation can improve clinical symptoms and heart function in patients with HD indicates that L-Carnitine treatment may have protective effects in heart patients on dialysis with carnitine deficiency [145,146], Carnitine treatment per HD session increased muscle carnitine concentration by threefold in hemodialysis patients [147], this is consistent with the results of the current study.

The transport of long-chain free fatty acids into the mitochondria by the carnitine shuttle plays a pivotal role in energy production through beta-oxidation [148]. Therefore, a deficiency in the level of carnitine in patients with HD leads to a defect in heart functions and muscle atrophy.

Higuchi et al., [146], reported beneficial effects of L-carnitine on cardiac function In HD patients with L-carnitine deficiency, this study is consistent with the results of the current study.

In a study by Silverman et al., L-Carnitine supplementation had a positive effect on maintaining ventricular compliance and myocardial contractility [149]. The results of this study which are in line with the results of the current study indicate that carnitine has a positive metabolic and functional effect on the myocardium, especially in patients with carnitine deficiency [150].

4.2. Effect of L-Carnitine Treatment on Body Mass Index in Chronic Kidney Disease Patients Undergoing Hemodialysis

Overweight and obesity are major health concerns worldwide and have been linked to a number of diseases [151], including diabetes, cardiovascular disease [152,153], especially kidney disease [154,155].

In this study, dialysis patients were divided according to BMI into four groups: less than normal (5%), normal weight (55%), overweight (22%), and obese (17.5%), as shown in the table [3-8].

Numerous studies have proven both In the United States [156] and the European [157], there is a close relationship between a high body mass index and the risk of developing chronic kidney disease [158].

The World Health Organization indicated in a report issued to it that more than (1.9) billion adults, aged 1s (18) years and over, suffer from overweight.

Lifestyle modifications including physical training, nutritional therapy, medication and surgery are common approaches to dealing with obesity [159,160], despite the availability of nutritional supplements to treat obesity, the effectiveness of most of them is still ambiguous [161,162].

It is suggested that the primary role of L-Carnitine in the treatment of obesity is through its effect on blood glucose control and lipid-lowering activities [163,164].

The current data in this study examining the effects of L-carnitine supplementation on weight loss indicated Inconsistent results (P = 0.197) as shown in the two figures [3-8], [3-9].

The results of the current study are consistent with the results of the study conducted by Kumar, Mechanick, and others in (2017), [165,166].

Therefore, the actual effect of carnitine supplementation on weight is still ambiguous, and other investigations and clinical trials have not been able to confirm its effect on body weight and need further clarification [167,168].

4.3. Effect of L-Carnitine Treatment on the Number of Hemodialysis Times Per Week in Patients with Hemodialysis

The primary goal is not only to keep dialysis patients alive but also to improve their quality of life and for this purpose additional treatment protocols are applied and L-Carnitine can also be included in this group [169].

In renal disease in its last stages before dialysis, carnitine levels increase by (50%) compared to healthy controls due to a decrease in kidney secretion and carnitine accumulation, but carnitine levels begin to decline after the start of dialysis [170].

It is known that long-term hemodialysis treatment is associated with a significant decrease in tissue and plasma L-carnitine levels [171]. The main reason for this is the removal of L-carnitine by dialysis, as it is a small molecule that is soluble in water and is freely washed out. This property makes dialysis patients predisposed to L-carnitine deficiency, as expected in our current study [172].

In this study, dialysis patients were divided in terms of the number of dialysis times per week into three groups: once a week (12.5%), twice a week (47.5%), three times a week (40%), as shown in the table [3-10].

Numerous studies have shown positive effects of carnitine in terms of nutritional parameters [173]. In another study, it was shown that L-Carnitine supplementation helps to improve many conditions that appear in uremic patients and there are reports that show an improvement in patients' subjective

complaints such as fatigue, fatigue, muscle pain, and spasms [174,175] in addition to other reports of recovery in laboratory parameters [176,177].

More patients who received L-Carnitine treatment have been judged that they had a significant improvement in their general health compared to what they were before treatment and this is consistent with the results of our current study.

The results of this study clearly showed that there is a significant difference (P = 0.004) in the number of dialysis times per week in treatment patients, compared to what they were before treatment, as shown in the two figures [3-10], [3-11].

During this study, patients who were treated with carnitine commented that they felt better and the patients noticed an improvement in their ability to walk long distances, increased appetite and physical endurance, as well as the ability to reduce the number of dialysis times per week and the number of hours of dialysis session, which they were not able to do before treatment with carnitine. Therefore, our study the current one is consistent with the study by Giorcelli and Corsi et al. [178].

CHAPTER Five

Conclusions

And

Recommendations

5.1. CONCLUSIONS

In summary, this study proved the following:

1. L-Carnitine deficiency is a common problem among individuals with chronic renal failure, especially dialysis patients.
2. L-Carnitine therapy is important in the treatment of anemia through its effective role in stabilizing the membranes of red blood cells and increasing their half-life
3. L-Carnitine deficiency in hemodialysis patients is considered one of the factors causing the development of heart disease and osteoporosis.
4. It Is important to give L-Carnitine treatment to dialysis patients, either orally or intravenously, every time dialysis Is performed to compensate for the deficiency of L-Carnitine in patients.
5. Follow-up of dialysis patients, especially those suffering from anemia and L-Carnitine deficiency.
6. Giving treatment to patients who underwent dialysis for the shortest period of time, between one and six months.
7. Avoid giving L-Carnitine treatment to HD patients who suffer from neurological attacks, blood allergies, and patients with hypothyroidism.
8. A study of longer duration in HD patients treated with L-Carnitine and compared with those with L-Carnitine deficiency who were not treated.

5.2. Recommendations

Future studies are recommended for the function of L-Carnitine therapy and its benefit for hemodialysis patients:

1- The use of L-Carnitine therapy in the treatment of patients with renal failure who are receiving dialysis.

2- Providing more medical units for dialysis.

3- Intensifying research regarding signs that reduce the risk of exacerbation of renal failure.

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الخلاصة

اجريت هذه الدراسة لمعرفة تأثير عقار L-Carnitine على مرضى الفشل الكلوي المزمن الخاضعين لغسيل الكلى. اشتملت الدراسة على 40 مريض تتراوح اعمارهم بين (62-21) سنة. تم تقسيم الدراسة الى مرحلتين المرحلة الاولى هي (ماقبل استخدام العلاج) والمرحلة الثانية (مابعد استخدام العلاج) .تم اعطاء علاج L-Carnitine Extra لمرضى غسيل الكلى بجرعة (1600) ملغ يوميا عن طريق الفم ولمدة ثلاث اشهر. اخذت العينات من مستشفى الامام الصادق التعليمي في محافظة بابل شعبة الكلية الصناعية (الديلزة) خلال الفترة الزمنية من 2022/8/14 (اغسطس) الى 2023/3/4 (مارس) , حيث تم قياس هرمون الغدد جار الدرقية PTH بواسطة تقنية ECLIAوباستخدام جهاز محلل المقايسة المناعية COPA من شركة Roche في سويسرا, وقياس كل من الكالسيوم والفوسفور بواسطة جهاز , spectrophotometer وقياس الالبومين بواسطة جهاز Human Star 300SRفي فرنسا, وقياس الهيموغلوبين بواسطة جهاز CBC Cell Tac في اليابان, وتم قياس انزيم CK بواسطة جهاز Fujifilm في اليابان.

توصلت الدراسة في نتائج التحليل الاحصائي ان هناك فرقا معنويا في هرمون الغدد جار الدرقية والكالسيوم والفسفور وكل من الالبومين والهيموكلوبين وانزيم الكرياتين كينيز لدى مرضى غسيل الكلى بعد استخدام العلاج مقارنة بمرحلة ماقبل العلاج, حيث لاحظنا انخفاضا في مستوى هرمون PTHو PO4وانزيم CK بعد العلاج , وزيادة في مستوى كل من Ca و Albumin و Hemoglobinلديهم مقارنة بما كانوا عليه ماقبل استخدام العلاج.

كما اضهرت نتائج الدراسة ان العلاج كان له تاثير واضح على مستوى البراميترات الحيوية لمرضى غسيل الكلى ذات الفترة الزمنية الاقل (مدة الاصابة بالمرض اقل من ثلاث الى ستة اشهر) , وكذلك المرضى الذين لديهم عدد جلسات غسيل كلوي اقل بالاسبوع من (1-2) مرة بالاسبوع.

خلال هذه الدراسة علق المرضى الذين عولجوا ب L-Carnitine انهم شعروا بتحسن في حالتهم الصحية ولاحظوا تحسنا في قدرتهم على المشي لمسافات طويلة وزيادة في التحمل البدني اضافه الى قدرتهم على تقليل عدد ساعات جلسة غسيل الكلى وهو ما لم يكن بمقدورهم القيام به ماقبل استخدام العلاج.

جمهورية العراق

وزارة التعليم العالي والبحث العلمي

جامعة كربلاء/كلية التربية للعلوم الصرفة

قسم الكيمياء

تأثير L-carnitine علئ بعض المؤشرات الحيوية في المرضى الذين يعانون من مرض الكلى المزمن

رسالة مقدمة الى

مجلس كلية التربية للعلوم الصرفة- جامعة كربلاء – كجزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

من قبل

أرتحام سعيد رحيم

اشراف

الاستاذ مساعد الدكتور
رحاب جاسم محمد

الاستاذ الدكتور
علي جاسم محيميد السلطاني

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