University of Kerbala

A Study of Thyroid and Parathyroid Hormones among Patients with AKI and CKD

A Thesis

Submitted to The Council of College of Education for pure Science University of Karbala /In Partial Fulfillment of the Requirements for the Degree of Master in Chemistry Sciences

By

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2022 A.D

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بسم الله الرحمن الرحيم

(يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَ الَّذِينَ أُوتُوا الْعِلْمَ دَرَجَات)

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Acknowledgments

Thanks Allah for giving me the power and willingness and for helping me during the period of study to perform this work in its form. My sincere thanks and deepest gratitude to my supervisors assistant professor Dr. Rehab Jassim Muhammad and assistant professor Dr. Ali Jasim Al-Sultani for their scientific guidance and helpful advice. Their efforts are deeply appreciated.

I'd like to express my heartfelt gratitude to the Deanship of the College of Education for Pure Sciences and the Department of Chemistry at the College for their unfailing support and assistance during the preparation and research years

I would like to express my deepest gratitude and respect to all participants in this study as patients and control persons. I am grateful to the staff members of Al-Imam Al-Sadiq teaching hospital for their valuable support.

I would also like to thank all my colleagues who supported me Throughout the research

Finally, If a word of gratitude should be said it should be to my family for their care and support, my deepest thanks to them

Sajad

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 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

Sajad

Summary

Background: Renal failure is classified into two types, acute kidney injury and chronic kidney disease. Acute kidney injury (AKI) is the sudden interruption of kidney function within a time of days, accompanied by a rise in serum urea and creatinine, and accumulation of nitrogenous waste products in a patient whose renal function was previously normal. While chronic kidney disease (CKD) is a deterioration in renal function occurs that classically develops over a period of months or years.

Objective: To evaluate of the association between the thyroid hormones (thyroxine (T4), triiodothyronine (T3)), thyroid stimulating hormone (TSH), and parathyroid hormone (PTH) and AKI and CKD.

Subjects and methods: This case- control study was conducted in Al-Imam Al-Sadiq Teaching Hospital in Babylon Governorate at period between October 2021 and April 2022, on sixty patients suffering from renal failure, 30 of them suffer from AKI and 30 others suffer from CKD in addition to 40 normal subjects as a control group. Their ages were ranged between 20-69 years. In terms of sex, 33 were males and 27 were females. Thyroxin, T3, TSH and PTH were measured using the enzyme-linked immunosorbent assay. The kidney function was estimated by determining the levels of urea and creatinine.

Results: The results of the study showed that there is an association between thyroid and parathyroid hormones with kidney failure diseases, a significant difference was found in T4, T3 and TSH levels the case and the control groups. Hypothyroidism led to an increase in TSH hormone and a decrease in T3, T4 levels in patients compared to the control group, and this is

accompanied by a decrease in the glomerular filtration rate (GFR). Hyperparathyroidism led to an increase in the secretion of PTH hormone, which is accompanied by hyperphosphatemia and hypocalcemia in patients compared with the control group (P= 0.01). Study results showed that the elderly people who suffer from AKI and CKD were more affected by the altered levels of the thyroid and parathyroid hormones.

Conclusions: Hypothyroidism and parathyroid function disorders are common among individuals with renal insufficiency, particularly those with end-stage renal disease. Hypothyroidism and hyperparathyroidism were the most prevalent and positively associated with increased age and decreased GFR. In patients undergoing HD treatment. It is important to do a regular examination of thyroid and parathyroid functions for patients with renal failure because early identification of thyroid disorders will help in better management of these patients.

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List of Abbreviation

The Term	Definition
ANF	Atrial natriuretic Factor
AKI	Acute Kidney Injury
BUN	Blood Urea Nitrogen
BMI	Body Mass Index
BMR	Basal metabolic rate
CKD	Chronic Kidney Disease
DIT	Diiodothyrosine
ELFA	Enzyme linked Flurecent Assay
EIA	Enzyme Immunoassay
ELISA	Enzyme-Linked Immuno Sorbent Assay
TFCs	Thyroid follicular cells
HPT	Hypothalamic- Pituitary-Thyroid
PTH	Parathyroid hormone
ESRD	End-stage renal disease
PRPP	5-Phosphoribosl -1-Pyrophosphate
TH	Thyroid Hormones
T_4	Thyroxine
TBG	Thyroxine Binding Globulin
LSD	Least Standard Deviation
m^2	Square meter
mm	Millimeters
ml	Milliliter
µl	Microliter
ng	Nanograms
nm	Nanometer
RBF	Renal Blood Flow
MIT	Monoidothyrosine
pg	Picogram
VC	Vascular Calcification
VSMC	Vascular Smooth Muscle Cells
GFR	Glomerular Filtration Rate

GI	Gastrointestinal
HOT	Hypothyroidism
SCH	Subclinical Hypothyroidism
P-value	Probability level of statistical
r	Correlation coefficient
RLUs	Relative Light Units
SD	Standard Deviation
TRH	Thyrotropin Relasing Hormone
T_3	Triiodothyroinine
TSH	Thyroid Stimulating Hormone
TG	Thyroglobulin
TTR	Transthyretion

Chapter one Introduction and Literature Review

1. Introduction and Literature Review

1.1.Kidney Disease

The kidneys are key organs in the human body. They account for only 0.5 percent of the body's total mass[1]. They are primarily responsible for the processing of urine, which serves as a medium for waste elimination, as well as the maintenance of acid-base balance, electrolyte balance, and blood osmolality[2].

There are around million nephrons in a single kidney, which are responsible for the entire glomerular filtration rate (GFR). In the event of a kidney injury, the kidney is capable of retaining GFR by hyperfiltration and compensatory hypertrophy of the remaining nephrons that are not ill [3]. The nephron's adaptability allows for the regular and continuous elimination of plasma solutes. Urea and creatinine levels begin to climb significantly only when the total GFR has decreased to 50%. Kidney function declines impede with their ability to keep their employment [4].

In healthy kidneys, the glomerular membrane prevents most proteins from going into the Bowman capsule, and the small amount of protein that is filtered is primarily reabsorbed by the renal tubules [5]. Glomerular membrane damage caused by inflammation or toxins causes it to leak, and the increased protein level in the filtrate overwhelms the kidney tubules' capacity to reabsorb protein. Protein loss in the urine causes a decrease in serum protein levels [6].

1.2.Renal Failure

Renal failure is described as the loss of kidney function [7]., which causes a reduction in (GFR) and the buildup of metabolites in the blood as a consequence of a disruption in the body's fluid balance, resulting in serious health problems [8], and therefore causes kidney damage in acute kidney injury (AKI) or chronic kidney disease(CKD) [9].

1.2.1.Acute Kidney Injury (AKI)

Acute kidney injury (AKI) is a rapid decrease in kidney function that can last from hours to weeks. AKI can be treated and kidney function restored, or it might worsen and progress to (CKD). It is characterized by a rapid loss of kidney function and the capacity to clear excess fluids and waste products from the blood [10]. AKI is linked to a high mortality rate and has an independent influence on the probability of dying. Dialysis is required for a significant proportion of AKI patients [11]. Symptoms such as reduced urine production, swelling in legs. shortness of breath, exhaustion, disorientation [12], and nausea may be an indication of acute renal failure (ARF), however ARF can also be discovered by lab tests performed for another reason [13].

1.2.1.1.Pathophysiology of AKI

AKI is classified into three types: prerenal azotemia (about 70%), intrinsic renal azotemia (about 25%), and postrenal azotemia (about 5%) [14], Prerenal azotemia is defined by a reduction in glomerular filtration rate (GFR) caused by a drop in renal perfusion pressure, with no injury to the renal parenchyma.

Acute urine flow blockage characterizes postrenal causes of acute kidney damage, Acute urine flow blockage characterizes postrenal causes of acute kidney damage [15], Urinary tracobstruction raises intratubular pressure, lowering GFR. Furthermore, acute urinary tract blockage can reduce renal blood flow and activate inflammatory processes, resulting in a decrease in GFR [16]. Intrinsic renal injury is classified into four types: Tubular injury (acute tubular necrosis), glomerular damage (Glomerulonephritis), interstitial damage, and vascular damage (all are possible). Figure 1-1 is a summary of the many forms of AKI [17]. The functions of oxidative stress and the inflammatory response in the pathogenesis of AKI are significant [18,19].

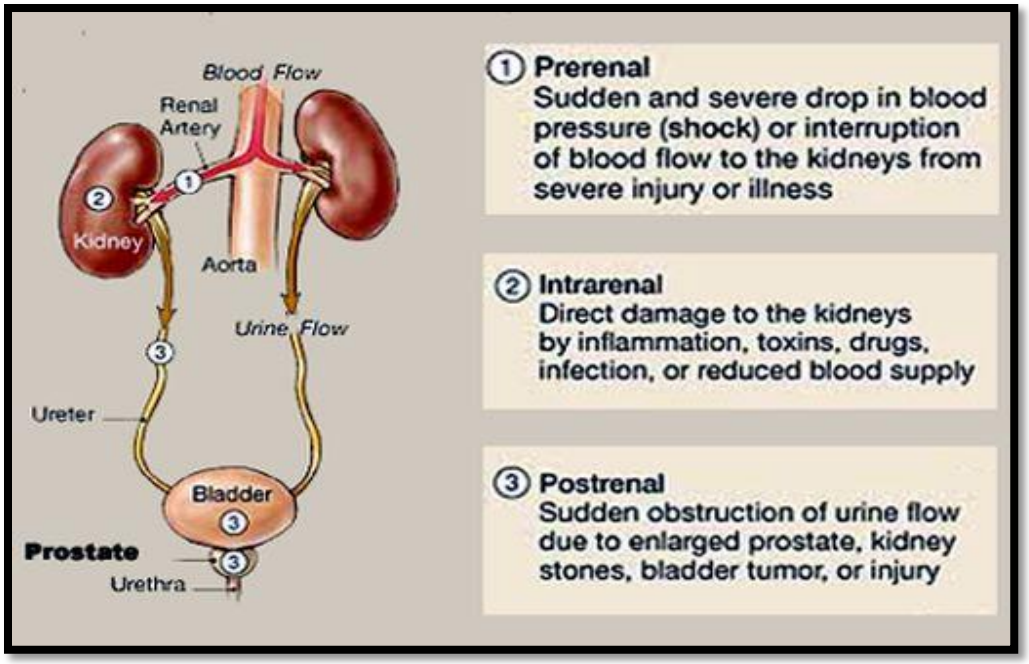

Fig. 1-1 **:** Definition and etiology of prerenal, renal, and postrenal azotemia [20].

1.2.2.Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD), sometimes referred to as end-stage renal disease (ESRD), is a common condition in which kidney function deteriorates over time [21]. It is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 mt^2 that persists for 3 months or more, regardless of the cause [22]. With the growth in the number of fatalities [23], about half of the patients are above the age of (40) years [24], It is a gradual decrease of kidney function that eventually necessitates the use of renal replacement therapy (dialysis or transplantation) [25] . Pathologic abnormalities in urine sediment, anomalies in urinary albumin excretion rates, or increasing urinary albumin excretion rates are all indicators of kidney injury [26].

1.2.2.1.Etiology of CKD

The causes of CKD vary widely, however the following are the most frequent main disorders that cause CKD and, eventually, end-stage renal disease (ESRD) [27].

- Type 2 diabetes mellitus (30 % to 50 %)
- Type 1 diabetes mellitus (3.9 %)
- High blood pressure (27.2 %)
- Glomerulonephritis with primary glomerulonephritis (8.2 %)
- Chronic tubulointerstitial nephropathy (3.6 %)
- Diseases that are inherited or cystic (3.1 %)
- Vasculitis or secondary glomerulonephritis (2.1 %)
- Neoplasma cell dyscrasias and neoplasms (2.1 %)

Prerenal (reduced renal perfusion pressure), intrinsic renal (pathology of the arteries, glomeruli, or tubules-interstitium), or postrenal (obstructive) disease processes can all induce CKD [28].

1.2.2.2.Pathophysiology of CKD

In contrast to acute kidney injury (AKI), when the healing process is complete with full functional kidney recovery, chronic and persistent insults from chronic and progressive nephropathies lead to progressive renal fibrosis and loss of the normal kidney architecture [29]. This affects the kidney's three compartments, namely the glomeruli, tubules, interstitium, and arteries. Histologically, it appears as glomerulosclerosis, tubulointerstitial fibrosis, and vascular sclerosis [30].

1.2.2.3.Renal Osteodystrophy

Renal osteodystrophy is a wide term that refers to all biochemical abnormalities and skeletal symptoms seen in individuals with chronic kidney disease or end-stage renal disease [31]. Derangements in calcium, phosphorous, PTH, and vitamin D blood levels, as well as their impact on bone turnover [32], mineralization, and extraskeletal calcifications, are all key components of this illness. According to reports, these anomalies are most likely to be noticed when the GFR is less than 60 mL/min/1.73 m2 [33,34].

1.3.Thyroid Gland

1.3.1.General Description

It is one among the body's largest endocrine glands, It is a shield-shaped structure placed in the lower neck anterior to the trachea between the

C5 and T1 vertebrae [35]. It produces T3 and T4 hormones that have an important effect in regulating metabolism, which we will discuss later [36]. The thyroid weighs 15–20 g and is heavier in men than in women; the thyroid weighs around 1 g as a baby and grows at a rate of roughly 1 g every year till the age of 15. It is a soft, reddish parenchymal organ in the shape of a H with two lobes (left and right) and one isthmus connects them Figure 1-2, it is covered with a fibrous layer and consists of two lobes each lobe is roughly 4 cm long, 2 cm wide, and 2–3 cm thick. The isthmus separating them is approximately 2 cm wide, 2 cm tall, and 2–6 mm thick. The normal blood ejection rate of fluid is about 5 ml / g from the thyroid gland every minute and about 1 liter per hour [37].

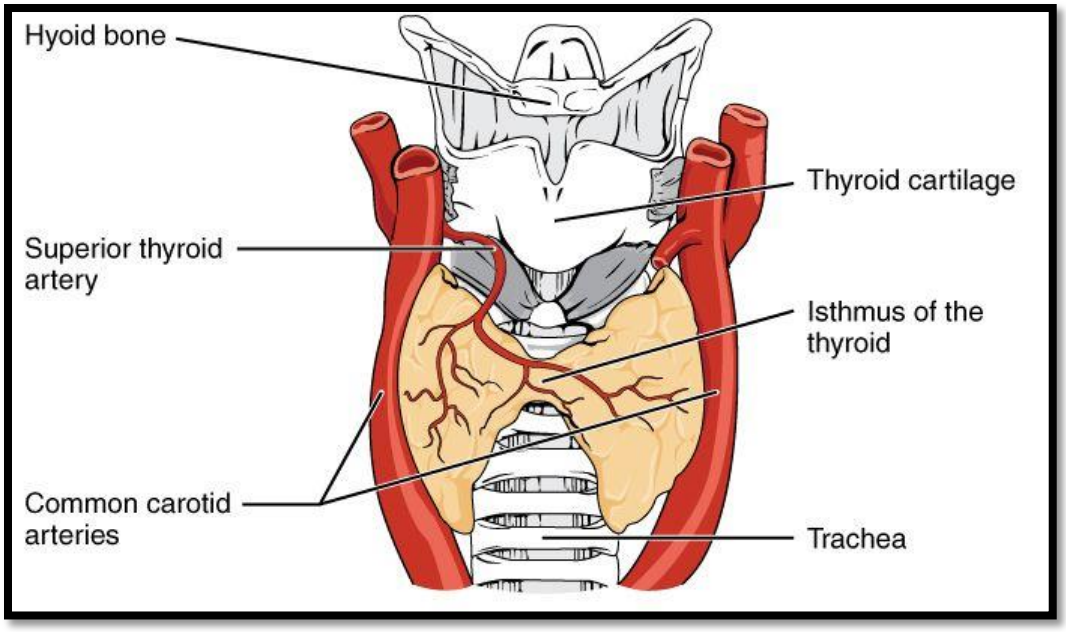

Fig. (1-2): Anatomy of thyroid gland [38].

1.3.2.Thyroid Regulation

The thyroid gland is an endocrine organ responsible for producing thyroid hormones [39]. The thyroid gland is regulated centrally by means of

the hypothalamic- pituitary-thyroid (HPT) -axis (upper panel), in short, involves hypothalamic release of thyrotropin-releasing hormone (TRH) in response to low levels of thyroid hormones in the circulation, through positive feedback [40]. This hormone is released into the blood, TSH which stimulate the thyroid gland to release hormones Thyroxine (T4) and 3,3′,5-triiodothyronine (T3) hormones and release them into the circulatory system. In the cells and tissues of the body the T4 is converted to T3 as shown in the figure 1-3. It is the derived from T4 or secreted as T3 from the thyroid gland, which is biologically active and influences the activity of all the cells and tissues of your body [41]. Organs such as the liver, kidney, and spleen convert up to 80% of T4 into T3. T3 is several time of stronger more potent than T4, T3 and T4 are synthesized from iodine and tyrosine [42]. These hormones have a negative effect on the hypothalamus and pituitary gland, increase levels of T4 and T3 hormones lead to a halt in the production of TRH from the hypothalamus and TSH from the pituitary gland. The thyroid also produces calcitonin, which plays a role in calcium homeostasis [43].

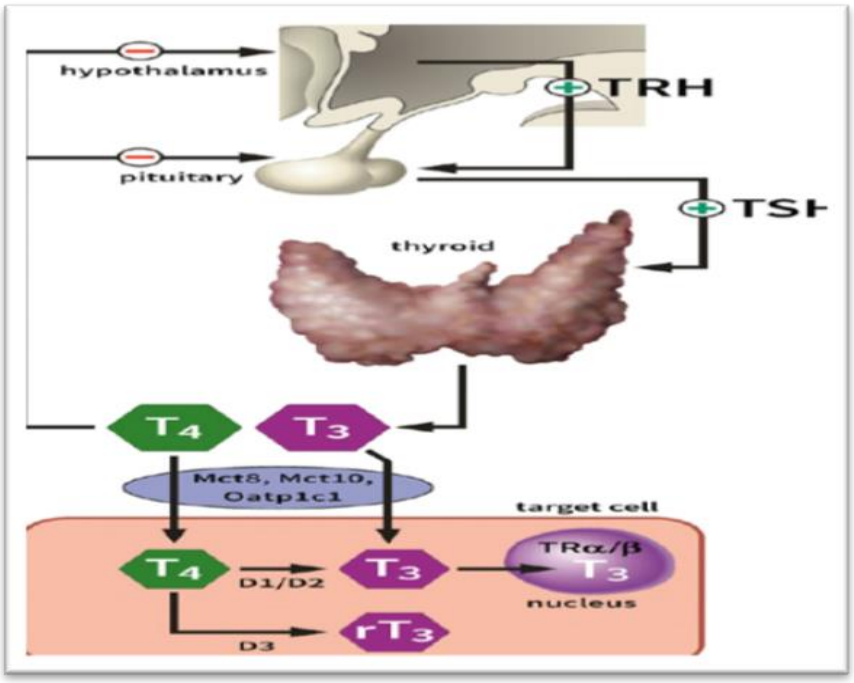

Fig. 1-3: Regulation of thyroid gland [40].

1.3.3.Thyroid Hormones:

1.3.3.1. Thyroid Hormones Synthesis:

Thyroid hormone synthesis depends on a number of follicles with walls that are formed from follicular epithelial cells and these follicles will be thyroid hormones and show the stages of hormone synthesis, which consists of three stages of iodine metabolism, thyroid globulin production, and the decomposition of tyrosine (Iodine is a key component of thyroid hormone biosynthesis) [44], as shown in the figure 1-4. In the first stage, the ingested iodide is absorbed in the small intestine and transported in plasma to the thyroid gland, where it is trapped and oxidized by the enzyme thyroid peroxidase, subsequently binding to tyrosine to form iodothyronines in thyroglobulin [45]. The iodide is entered into the thyroid cells through the I Na co-transport channel, then the iodide goes to the lumen or colloidal area

to be converted from iodide to iodine by the enzyme Thyroperoxidase. Thyroid follicular cells (TFCs) secrete thyroglobulin (TG), Which is a very important protein that contains the amino acid Tyrosine, Where it is secreted by thyroid cells to lumen so that iodine is added to the thyroxine in thyroglobulin by a special enzyme thyrioperoxidase. Iodination produces mon-iodotyrosine (MIT,T1) and di iodotyrosine (DIT, T2), the Di iodo tyrosine (DIT) is linked with mono iodo tyrosine(MIT) to form T3 through a process called Organification [46]. Di iodo tyrosine (DIT) is also linked with Di iodo tyrosine(DIT) to form T4 through a process called coupling reaction, T3 and T4 are linked with the large structure of thyroglobulin, so the thyroglobulin bound- iodine is returned to the thyroid cells by the process of endocytosis, where it is broken down or decompose by Lytic enzymes to release T3 and T4 as shown in the figure 1-5, after which they are secreted into the bloodstream by TSH [47].

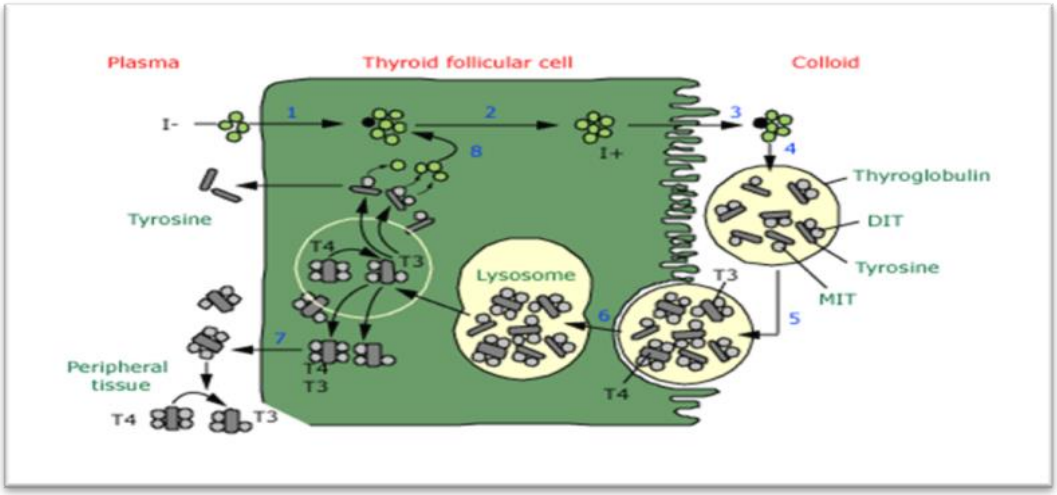

Fig. 1-4: Thyroid hormone biosynthesis [46].

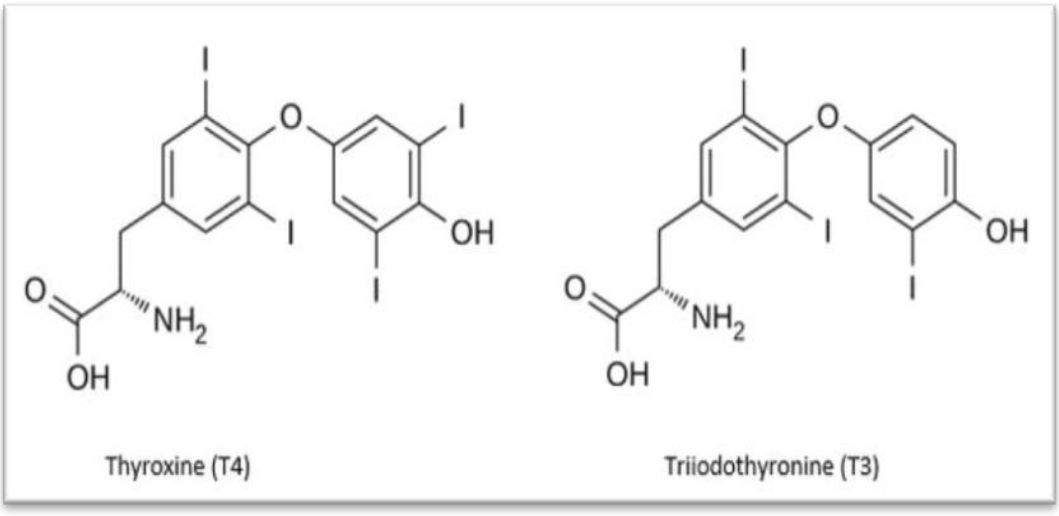

Fig. 1-6: Chemical structure of thyroid and parathyroid hormone [47].

1.3.3.2. Transport of Thyroid Hormones

Thyroid hormones are carried in the blood via three proteins: albumin, which has a high capacity but a low affinity, transthyretin (TTR), which has a medium capacity but a high affinity, and thyroxin cartage globulin (TBG), which has a low capacity but a high affinity [48]. TBG, TTR, and albumin are the most major human thyroid hormone binding proteins, Lowercase T4 and T3 are unbound, yet at the tissue level, it is this free hormone that is metabolically active hence in charge of thyroid function [49,50].

1.3.4.Thyroid Disorders

1.3.4.1. Hypothyroidism

Hypothyroidism is a chronic condition characterized by a lack of thyroid hormones thyroxine (T4) and triiodothyronine (T3) [51]. This only generates a trace quantity of T3 [52]. Only around 20% of T3 in peripheral tissue is produced by the thyroid gland, with the remainder generated from

the enzymatic conversion of T4 to T3 inside the target tissues. Infertility, cardiovascular illness, and neurological and musculoskeletal problems are among outcomes of untreated or improperly managed hypothyroidism [53]. The most common cause of thyroid problems, including hypothyroidism, is a lack of iodine in the environment, globally [54], but autoimmune thyroiditis (Hashimoto's disease) is the most common cause of primary hypothyroidism in areas of iodine sufficiency [55]. A failure of the thyroid to generate T4 and T3 induces the pituitary to create more thyroid-stimulating hormone (TSH) via a negative feedback process . Hypothyroidism is caused in more than 99 percent of cases by a failure of the thyroid gland to generate thyroid hormones (primary hypothyroidism) [56]. The other 5% of patients suffer hypothyroidism from other causes, such as secondary hypothyroidism produced by pituitary gland underproduction of TSH, tertiary hypothyroidism caused by thyrotropin-releasing hormone shortage, and peripheral (extra-thyroidal) hypothyroidism . Less than 1% of cases are due to central hypothyroidism, which includes secondary and tertiary hypothyroidism, and peripheral hypothyroidism.

1.3.4.1.1.Subclinical Hypothyroidism

Subclinical hypothyroidism is characterized as an increase in serum TSH levels (normal range 5-10 IU/mL) in the presence of normal serum free T4. The frequency of subclinical hypothyroidism rises in tandem with the fall in GFR. According to one study, roughly 18% of CKD patients who do not require dialysis had subclinical primary hypothyroidism. This observation is related with a gradual decrease in estimated GFR. The incidence of subclinical primary hypothyroidism rose from 7% to 17.9% in those whose GFR dropped from 90 mL/min to 60 mL/min [52]. Some

researches claimed that hypothyroidism in uremic dialysis patients can be treated with dietary iodine restriction, reducing the requirement for hormone replacement medication.

1.3.4.2. Hyperthyroidism

This type of thyroid disorder is characterized by hyperthyroidism, also known as thyrotoxicosis, with an increase in T3 and T4 production, excitability in the T3:T4 ratio, and inhibition of levels of the hormone thyrotropin, as well as distinct medical symptoms. The main factor is either due to the breakdown of the thyroid follicles. Furthermore, hyperthyroidism develops as a result of excessive thyroid hormone treatment resulting in the release of high physiological levels of T3 and T4, which causes a foul mouth odor induced thyroiditis [57].

1.3.4.2.1. Subclinical Hyperthyroidism

Subclinical hyperthyroidism is a condition in which there is a low level of thyroid stimulating hormone (TSH) but normal fluid thyroxin and triiodothyronine levels, is prognosis whenever serum sensitive TSH is suppressed beneath 0.1IU/mL and serum free thyroxin and triiodothyronine echelons are common, Subclinical hyperthyroidism in males over the age of 65 has been related to a higher risk of frailty [58]. Patients over the age of 65 who have a subclinical hyperactive thyroid gland are typically asymptomatic [59], However, younger people may experience modest adrenergic symptoms [60]. It is critical to note that hyperthyroidism can actually hasten CKD. The following are the mechanisms:

(i) In hyperthyroidism, increased renal blood flow causes intraglomerular hypertension, which leads to increased filtration pressure and subsequent hyperfiltration. Proteinuria is known to cause direct renal injury in hyperthyroidism.

(ii) Increased mitochondrial energy metabolism combined with downregulation of superoxide dismutase, which occurs in hyperthyroidism, contributes to increased free radical generation, which causes renal injury.

(iii) Oxidative stress also contributes to hypertension in hyperthyroidism, which contributes to CKD progression.

1.4. Anatomy of the Parathyroid Glands

There are generally two pairs of parathyroid glands (inferior and superior). The parathyroid gland is oval or bean shaped, measuring 6 mm 4 mm 2 mm and weighing 40 mg to 60 mg [61]. The average person has four parathyroid glands. The superior parathyroid glands are normally positioned dorsal to the RLN at the level of the cricoid cartilage, whereas the inferior parathyroid glands are placed ventral to the nerve [62]. They are frequently surrounded with fat and might be difficult to distinguish from it .The parathyroid glands' blood supply is generally supplied from inferior thyroid artery branche. A thin fibrous capsule surrounds the parathyroid glands, splitting them into lobules [63]. The stromal fat around the parathyroid glands steadily rises with age, reaching 30% by age 25. In preadolescence, the parathyroid glands are mostly composed of main cells that generate parathyroid hormone (PTH) [64]. The chief cells are important in calcium homeostasis because they detect changes in extracellular calcium

concentration and release the proper amount of PTH to restore or maintain normal blood calcium levels [65].

1.4.1.Parathyroid Hormone (PTH)

PTH, also known as parathormone or parathyrin, is a peptide hormone released by the parathyroid glands that controls blood calcium concentrations through its actions on bone, kidney, and gut [66]. It is a prohormone that is a polypeptide with 84 amino acids. It has a molecular mass of around 9500 Da. PTH has an effect on bone remodeling, which is a continuous process in which bone tissue is resorbed and regenerated over time. In reaction to low blood serum calcium (Ca^{2+}) levels, PTH is released. PTH indirectly increases osteoclast activity inside the bone matrix (osteon) in an attempt to release more ionic calcium (Ca^{2+}) into the blood in order to increase a low serum calcium level. The bones serve as a (metaphorical) "bank of calcium" from which the body may make "withdrawals" as needed to maintain adequate calcium levels in the blood, PTH is predominantly released by the parathyroid gland's primary cells. The hormone calcitonin works against it. PTH receptors are classified into two categories. PTH 1α receptors, which are triggered by the 34 N-terminal amino acids of PTH, are abundant on bone and kidney cells. Thyroid hormone 2 receptors are abundant on cells in the central nervous system, pancreas, testes, and placenta, PTH has a half-life of roughly 4 minutes. Bone disease, hypocalcemia, and hypercalcemia can be caused by disorders that produce too little or too much PTH, such as hypoparathyroidism, hyperparathyroidism, and paraneoplastic syndromes. The function of PTH involves serum calcium regulation, serum phosphate regulation, and vitamin D synthesis. PTH increases the activity of the enzyme 1αhydroxylase, which

in the kidney transforms 25-hydroxycholecalciferol, the primary circulating form of inactive vitamin D, into 1,25-dihydroxycholecalciferol, the active form of vitamin D [67].

1.4.2. Parathyroid Disorders

1.4.2.1. Hyperparathyroidism

Hyperparathyroidism is classified as primary, secondary, or tertiary dysfunction.

Primary hyperparathyroidism is caused by a parathyroid gland anomaly, such as an adenoma or hyperplasia, which causes the gland to oversecrete. This is characterized by high PTH levels [68], hypercalcemia, and hypophosphatemia in test results. A mutation of the calcium-sensing receptor in the parathyroid gland and kidney causes a lack of regulation of PTH release until a higher level of blood calcium, resulting in greater bone resorption and hypercalcemia in familial hypocalciuric hypercalcemia. Hypercalcemia is aggravated further by increased renal calcium absorption, leading in hypocalciuria, which can produce symptoms such as excessive thirst and urination, constipation, bone pain, weariness, depression, and even kidney stones. This is usually remembered as "stones, bones, moans, thrones, and psychiatric overtone" [69].

Secondary hyperparathyroidism is the oversecretion of PTH in reaction to unusually low calcium levels in the blood caused by various clinical processes such as renal failure, gastrointestinal malabsorption, or simply a vitamin D deficiency. The lab values vary depending on the underlying disease. PTH levels will be increased in chronic renal failure,

although calcium and phosphate levels will be lower. PTH will be high in the presence of malabsorption and vitamin D insufficiency, whereas calcium and phosphate will be lowered [70].

Tertiary hyperparathyroidism is extremely rare, however it can occur in the setting of ongoing PTH production even after a secondary hyperparathyroidism triggering illness has been cured. PTH levels will be somewhat increased, calcium levels will be normal or raised, and phosphate levels will be low [70].

1.4.3.PTH Hyporesponsiveness in Chronic kidney Disease

In CKD, the bone and renal responses to PTH activity become increasingly reduced, a phenomenon known as PTH resistance. Because the reaction to PTH is muted but not absent, we believe the term hyporesponsiveness is more accurate. Aging, black race, and diabetes are all related with PTH hyporesponsiveness. PTH hyporesponsiveness in CKD is not a new notion, however it is undervalued in the nephrology community. Furthermore, its pathophysiology is complicated and only partially understood. Phosphate loading, calcitriol insufficiency, oxidative stress, aluminum overload, magnesium deficit, buildup of PTH fragments, and uremic toxins are all causes [71].

1.4.4.The Effect of PTH on Bones

Increased levels of parathyroid hormone (PTH) play a significant role in the pathophysiology of high bone turnover conditions. Primary, secondary, or tertiary hyperparathyroidism can occur [72]. Tertiary hyperparathyroidism can be caused by tumors of the parathyroid glands that

secrete PTH on their own. The most common cause of osteodystrophy is secondary hyperparathyroidism [73]. In the etiology of renal osteodystrophy, the several variables implicated in the route leading to secondary hyperparathyroidism are also worth mentioning: [74] .

Phosphate retention: Excess phosphate in the blood can promote PTH production in a variety of ways. It can either directly raise PTH mRNA levels or reduce calcium and calcitriol levels, resulting in a rise in PTH levels.

Calcium: There is a well-established link between calcium and PTH levels. A reduction in blood calcium stimulates PTH secretion as well.

Calcitriol's Function: Calcitriol and PTH both raise serum calcium levels, and when calcitriol levels fall, secondary hyperparathyroidism develops as a result of reduced calcium absorption via the gut and a reflex rise in PTH. Calcitriol is also necessary for the parathyroid glands to decrease PTH production [33].

Osteoclasts, which tear down or resorb bone, and osteoblasts, which build up or make new bone, are the two primary cells involved in this process. PTH, vitamin D [75], and acidosis are factors that activate the complex and attempt to boost osteoclast development. By increasing bone resorption, blood calcium levels will rise [76], Osteoprotegerin is an osteoclastogenesis inhibitor that reduces bone resorption. Low bone turnover states [77], on the other hand, have lower than normal PTH levels, rendering the bone incapable of integrating calcium into the new bone that is being created [78].

1.4.5. Parathyroid Gland Physiology, Calcium and Phosphate Homeostasis

Parathyroid hormone regulates extracellular calcium homeostasis. CaSR, a G protein coupled receptor found on the surface of parathyroid cells, detects these variations in blood calcium levels1 [79]. A drop in extracellular calcium levels lowers CaSR signaling via G11 and Gq, resulting in an increase in PTH release from the parathyroid glands. PTH released into the circulation activates on the G protein coupled PTH1 receptor (PTH1R) [80], in bone and the kidneys to raise serum calcium levels, resulting in feedback regulation of PTH production from the parathyroid glands [79]. PTH is also involved in the regulation of circulatory phosphate levels. Indeed, an increase in circulating phosphate levels promotes PTH production, which then works on the kidneys to impede tubular phosphate reabsorption [81]. Fibroblast growth factor 23 (FGF23) is an osteocyte-derived hormone that inhibits renal tubular phosphate reabsorption and the renal production of calcitriol also known as 1,25dihydroxyvitaminD (1,25(OH) 2D) [82]. In the setting of hypoparathyroidism, the absence or low circulating levels of PTH cause hypocalcaemia by affecting osteoclast activity, which reduces calcium efflux from bone, increasing urine calcium excretion, and blocking the renal calcitriol synthesis, which reduces dietary calcium absorption in the intestine [83]. PTH deficiency also produces hyperphosphataemia due to an increase in renal tubular reabsorption of phosphate, and chronic hyperphosphataemia has been linked to increases in serum FGF23 levels in hypoparathyroid patients [61], PTH also has a role in magnesium homeostasis. PTH enhances magnesium reabsorption in the kidney [84], whereas severe and persistent hypomagnesaemia causes

hypocalcaemia by inhibiting PTH production and increasing PTH endorgan resistance [85,86]. Hypermagnesaemia may also limit PTH release by activating CaSR, resulting in hypocalcaemia [87].

1.5.Biochemical Phenotype Parameters

1.5.1.Urea

Urea is a tiny molecule that is water soluble. It is made up of two nitrogen atoms. It is the end result of nitrogen and protein metabolism. It is the component with the greatest blood level in uremia patients [88]. Urea, a colorless crystalline component with a molecular weight of 60,056 daltons, is the major nitrogenous by-product of protein processing in the liver. Because it is normally filtered outside the body by the renal system, it is critical to check its blood level because unusual levels may indicate various illnesses such as kidney or liver disease. It is an excellent indicator of dialysis adequacy [89].

Carbamylation normally rises when renal function diminishes, followed by urea buildup. Because urea synthesis is directly proportional to protein consumption, dietary restriction contributes to a reduction in urea production. Urea per se is likely to be implicated in CVD, development of CKD, anemia and intestinal disease, and leads to an accelerated aging phenotype overall.

1.5.2.Creatinine

Creatinine is produced in the muscle by a nonenzymatic phosphocreatine breakdown. It is carried to the kidneys via the circulation, where the majority of it is filtered and excreted in the urine[90], Skeletal

muscle releases creatinine at a constant pace. Its serum level is strongly linked to skeletal muscle. The glomerulus filters it, and the proximal tubule secretes a tiny quantity into the glomerular filtrate. Increased creatinine levels in healthy people may be attributed to muscle mass gain and a high protein diet. Its high serum levels were detected in more males than females, which might be attributed to masculine muscular bulk (male: 20-25; female: 15-20 mg / kg / day) [91].

The quantity of creatinine in the blood is determined by its generation, glomerular filtration, tubular secretion, age, gender, race, body habits, cuisine[92], and individual physical state are all factors that influence creatinine levels. When creatinine levels rise, itching and nerve ending damage might occur.

1.5.3.Calcium

It is the fifth most plentiful element after oxygen, carbon, hydrogen, and nitrogen. It has a structural purpose and is a necessary component of bones and teeth. It is a "second messenger" that impacts enzyme performance and hormone production, including insulin, aldosterone, vasopressin, and rennin. It is required for cell metabolism, neuronal communication, and muscle contraction. Furthermore, it performs a variety of activities in neurotransmitter generation, release, and receptor responsiveness [93]. Concerning blood calcium, it is represented in three forms: one bound to plasma protein (40 %), another made a chelate with serum anions around (10%), and the third is the active and more vital free ionized calcium (Ca^{2+}) approximately (50%) [94].

In the absence of adequate dietary calcium intake, circulatory calcium levels are tightly controlled by the parathyroid hormone (PTH) and vitamin D at the expense of the skeleton. A decrease in Ca^{2+} causes PTH release in the blood. PTH initiates bone resorption, a method in which activated osteoclasts break down and release $Ca2^{+}$ into the blood [95].

Mineral and bone metabolism disturbances in CKD patients are suspected of causing vascular calcification (VC). As kidney function declines, phosphate binds to calcium in the blood, When calcium/phosphate particles in the serum exceed their saturation limit, they precipitate and stimulate the vascular smooth muscle cells (VSMC) of the arteries to undergo dedifferentiation, causing the VSMC to calcify and stiffen. Trials to ban VC in CKD were therefore based on the concentrations of calcification stimulators (phosphate and calcium) and inhibitors, Changes in biomarkers of bone disease such as calcium, phosphorus, alkaline phosphatase (ALP), and PTH can be associated with morbidity, cardiovascular effects, and mortality in dialysis patients with CKD [96]. Nowadays, bone disease is common in CKD patients. Several bone problem treatment guidelines have been published, all of which confirm the importance of monitoring calcium, phosphorus, and PTH levels in people with CKD [97].

1.5.4.Phosphorus

Phosphorus is a mineral that is abundant in humans. It is found in both organic and inorganic forms, but only the inorganic form is measured. Inorganic phosphorus in bone serves as structural body support [98].

Phosphorus is used in the creation of creatine phosphate, which is involved in several energy tasks such as muscular contraction, neurological

functioning, and electrolyte transfer. It is absorbed in the small intestine by paracellular and active transport. A variety of variables regulate tubular reabsorption via sodium phosphate cotransporters found in tubular cell membranes [99]. Its reabsorption can be reduced owing to a high food consumption, acidosis, PTH, or glucocorticoid medication. The kidney is the primary metabolic regulator. 85 % of phosphorus is found in bone, mostly as hydroxyapatite, 14 percent is found in cells, and less than one percent is found in plasma. Acid-base balance, hormones, and vitamin D all influence phosphorus absorption and reabsorption in the intestine and the kidney [100].

High serum phosphate and PTH levels may contribute to the accelerated development of CKD, although the causes are unclear [101]. Among the underlying processes are vascular and renal tubular calcification, which cause cell injury and fibroblast growth. Another proposed mechanism is phosphate-mediated endothelial damage [102]. Hyperphosphatemia is announced to increase the risk of cardiovascular episodes resulting from VC in patients with CKD and bone disorders and to affect bone lesions, Elevated cardiovascular death in dialysis individuals is linked with hyperphosphatemia [103].

1.6. The Aims of the Study

1- Evaluation of thyroid hormones T3, T4 and TSH in AKI and CKD patients and comparing with healthy group

2- Evaluation of parathyroid hormone PTH in AKI and CKD patients and comparing with control group

3- Evaluation of calcium and phosphorous in AKI and CKD patients and control group

4- correlation between thyroid and parathyroid hormone for AKI and CKD patients

CHAPTER TWO

MATERIALS and METHODS

2. 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	Source
Calcium determination kit.	Egyptian Company for Biotechnology (S.A.E) (Egypt)
Creatinine kit	Bio system
Parathyroid hormone Kit	Roche – Switzerland
Phosphorous determination kit.	Spinreact (Spain).
Total thyroid stimulating hormone ELISA Kit	Biomereux, US
Total Thyroxin ELISA Kit.	Biomeraux, US
Total Triiodothyronine ELISA Kit.	Biomeraux, US
Urea kit.	Architect, Abbott laboratories US
Uric acid kit.	Architect, Abbott laboratories, US

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	Suppliers
Absorbance ELISA microplate reader	Bio Teak
Centrifuge	Heraeus, (Germany)
Micropiptte 10-100µL	Slamed (Germany)
Mini Vidas	France
Shakers	Japan
Spectrophotometer type21	Miltion Roy (Switzerland)
Water bath	Slamed (Germany)

2.1.3. Subjects:

The study subjects were divided into three groups :

1- Control group : included forty (40) supposed healthy subjects who were aged (20-69) years.

2- Chronic renal failure group : included thirty (30) patients with chronic renal failure aged (20- 69) years.

3- Acute kidney injury group: included thirty (30) patients with acute kidney injury aged (20-69) years.

These patient was diagnosed by specialist doctor (Dr. Ali Jassim Al Sultani) who had a medical decision to undergo a renal disease's

Sixty patients (33 men and 27 women) were admitted to Babylon Governorate's Al-Imam Al-Sadiq Hospital. The study comprised 60 samples of patients with renal failure, 30 samples from patients with acute renal failure, and 30 samples from patients with chronic renal failure. Aside from the control group, which included 40 blood samples. Males and females ranging in age from 20 to 69 years old were researched. All of the information gathered was provided in the form of age, weight, height, smoking, blood pressure, kind of disease, time period, blood diseases, diabetes, therapy, and have or not kidney stones.

2.1.4. Design of study

The study was conducted at Imam Sadiq Teaching Hospital , and specialist clinicals at period between (October 2021) to (April 2022). It included (100) subjects , (control 40 and patients 60) as shown in Table 2-1

Table 2-3: Data of patient's and control groups:

Subjects	**No.**
Patients of CKD	30
Patients of AKD	30
Controls	40
Total	100

2.1.5. Exclusion Criteria:

Subjects with any chronic condition, as well as smokers, pregnant women, and those with cancer, were excluded from this study.

2.1.6. Blood and Serum Preparation:

The vein is employed in the area just in front of the forearm. The arm is stretched, (10 cm above the elbow) is tightened. Sterilization of the skin over the vein is required. A sterile disposable needle is placed into the vein, and the plunger of the syringe is slightly withdrawn. The tourniquet is removed if blood emerges. Using sterile disposable syringes, a venous blood sample (5 cm^3) was taken from each patient and control group. The needle is removed from the syringe, and the blood is transferred slowly. to free a tube an anticoagulant. After allowing the blood to clot for 15 minutes, the clot removed and serum was be recovered by centrifuging for 5 minutes at a relative centrifugal force. The sample(s) were kept at -20°C temperatures for

up to 45 days. It is best to avoid using infected devices as well as freezing and thawing.

2.2. Methods:

2.2.1. Measurement of Body Mass Index:

Body mass index was calculated from the following equation:

BMI = Weight (kg)/Height (m^2)

BMI is classified as follows.<18.5 kg/m2 underweight, 18.5-24.9 kg/m2 normal weight, 25-29.9 kg/m2 over weight, 30.0-34.9 kg/m2 obese Class I, 35.0-39.9 kg/m2 obese Class II, and >40.0 kg/m2 obese Class III (according to the WHO)

2.2.2.Thyroid stimulating hormone (TSH) level determination:

Thyrotropin stimulating hormone level was measured using the ELISA kit from Biomereux, US.

2.2.2.1. Principles:

The TSH test is a two-step immunoassay that uses chemiluminescent magnetic microparticle immunoassay (CMIA) technology with chemiflex assay procedures to evaluate the presence of thyroid stimulating hormone (TSH) in human serum.

1-Sample anti-TSH antibody coated paramagnetic micro particles were mixed with TSH test diluent. TSH binds to anti-TSH antibody coated micro particles in the samples.

2- After washing, the reaction mixture was supplemented with an anti-TSH acridinium-labeled conjugate.

3- Following another wash cycle, Pre-Trigger and Trigger solutions were added to the reaction mixture.

4-The chemiluminescent reaction that resulted was quantified in units of relative light (RLUs).The amount of TSH in the sample and the RLUs identified by the architect system optics had a direct link.

2.2.2.2. Reagents:

Kit Contents

Architect TSH 7K62

Micro particles: Anti-TSH (mouse, monoclonal) coated micro particles in TRIS buffer with protein (bovine) stabilizers 0.07 percent solids is the minimal concentration antibacterial agents as a preservative

Anti-TSH (monoclonal mouse) coated microparticles in MES buffer with protein (bovine) stabilizers, 60 ng/ml is the minimal concentration. antibacterial agents as a preservative

Assay diluent: TSH assay diluent in TRIS buffer.

Preservative: antimicrobial agents.

2.2.2.3. Assay Procedure:

To suspend the microparticles, the bottle was combined. Micro particles that may have collected during shipment should be removed before putting the

reagent kit into the device for the first time. No additional mixing is necessary after the micro particles have been inserted the first time.

1- The micro particle bottle were Inverted to 30 times.

2- The bottle was inspect to ensure micro particles were suspended. If micro particles are still adhered to the bottle continue to invert the bottle unit the micro particles have been completely suspended.

3-If the micro particles do not suspend, it do not use, constancy local Abbott representative.

4-Once the micro particles have been suspended, a septum on the bottle was placed, For instructions about placing septum's on bottles, refer to the reagent handing section of this package insert.

5- The reagent kit were loaded on the architect I system.

6-Verify that all necessary reagents were presented.

7- Septum's were presented on all reagent bottles that is necessary.

8- Calibration was order , if necessary.

2.2.2.3. Calculation:

A does respond curve was used to ascertain the concentration of thyrotropin in serum exemplification.

1-The absorbance acquired from the microplate literary critic printout was recorded.

2-On linear graph paper, plot the absorbance of each calibrator vs the corresponding thyrotropin concentration in IU/mL.

3-A best-fit curve was constructed through the depicted points.

4-To estimate the concentration of thyrotropin in serum specimens, the absorbance of each specimen was plotted on the vertical axis of the graph to find the crossing point on the curve and the concentration (µIU/ml) plotted on the horizontal axis of the graph. As shown in the figure 2-1

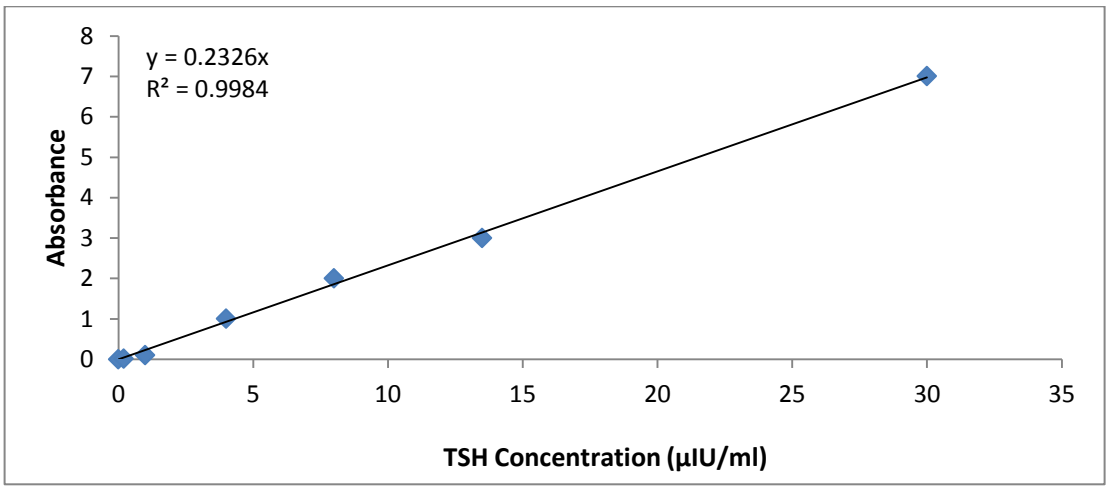

Fig. 2-1: Standard curve of determination of (TSH) concentration.

2.2.3. Determination of Total Thyroxine (T4) Hormone Level.

Total thyroxine T4 level was determined by the method of the kit Biomereux, US.

2.2.3.1. Principles :

The architect total T4 assay is a two-step immunoassay to determine the presence of thyroxine (Total T4) in human serum using chemiluminescent magnetic microparticle immunoassay (CMIA) technology with flexible assay protocols referred to as chemiflex.

1-Sample anti-T4 coated paramagnetic micro particles were combined. Bound T4 is removed from the binding sites on thyroxin binding globulin, prealbumin and albumin. T4 binds to the anti-T4 coated micro particles in the sample.

2-A reaction mixture was formed by adding T3 acridinium-labeled conjugate after washing.

3-Pre-Trigger and Trigger solutions were added to the reaction mixture after another wash cycle.

4-The ensuing chemiluninescent reaction was quantified in terms of relative light units (RLUs). The amount of total T4 in the sample and the RLUs identified by the architect I system optics had a direct link.

2.2.3.2. Reagents:

Kit contents

Architect Total T4 7k66

Micro particles: Anti-T4 (sheep) coated micro particles in TRIS buffer with sheep IgG stabilizers. Minimum concentration :0.05% solids. Preservative: Sodium azide.

Conjugate: T3 acridinium- labeled conjugate in MES buffer with Nacl and Triton X-100 stabilizers. Minimum concentration: 0.2 ng/mL. preservative: proclin.

2.2.3.3. Assay Procedure:

Before the reagent kit is loaded onto the system for the first time, the micro particle container must be mixed to suspend any micro particles that

may have collected during shipment. No additional mixing is necessary after the micro particles have been inserted the first time.

1- For 30 seconds, the micro particle container was inverted.

2- The bottle was examined to confirm that tiny particles were suspended. If the micro particles are still stuck to the container, continue to flip it until the micro particles are entirely suspended.

3- It not use if the micro particles do not suspend; instead, contact your local Abbott representative.

4- After the micro particles were suspended, a septum was attached to the bottle.

5- The architect I system was loaded with the reagent kit.

6- Confirm that all essential reagents were provided.

7- It ensures that septums were clearly visible on all reagent bottles.

8- If calibration was required, it was ordered.

2.2.3.4. Calculation:

To construct a calibration curve, the architect total T4 assay employs a four parameter logistic curve fit data reduction approach (4PLC, Y-weighted).

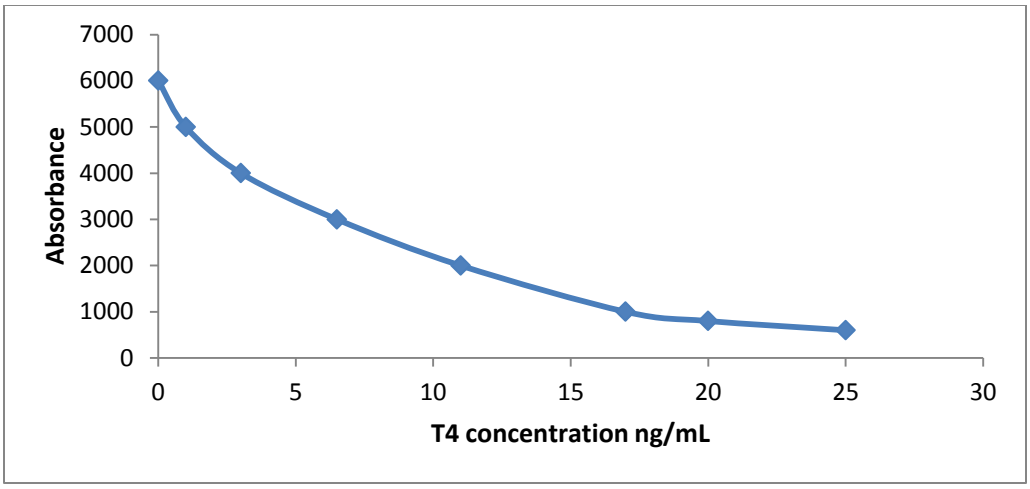

Fig. 2.2: Standard curve of determination of (T4) hormone concentration.

2.2.4. Determination of Total Triiodothyronine (T3) Hormone Level.

Total Triiodothyronine T3 level was determined by the method of the kit Biomereux, US.

2.2.4.1. Principles :

The architect total T3 test is a two-step immunoassay that uses chemiluminescent magnetic microparticle immunoassay (CMIA) technology with chemiflex assay procedures to assess the presence of Total T3 in human serum.

1-A single sample of anti-T3 coated paramagnetic micro particles was mixed. T3 binds to the anti-T3 coated micro particles in the sample.

2-A reaction mixture was formed by adding T3 acridinium-labeled conjugate after washing.

3-After another wash cycle, the reaction mixture was treated with Pre-Trigger and Trigger solutions.

4-The ensuing cherniluminescent reaction was quantified in terms of relative light units (RLUs). The amount of total T3 in the sample has an inverse connection with the RLUs identified by the architect I system optics.

2.2.4.2. Reagents:

Kit contents

Architect Total T3 7k64

Micro particles: Anti-T3 (sheep) coated microparticles in TRIS buffer containing sheep IgG stabilizers. 0.05 percent solids is the minimum concentration. Sodium azide is a preservative.

Conjugate: T3 acridinium-labeled conjugate in MES buffer with stabilizers Nacl and Triton X-100. 0.33 ng/ml is the minimum concentration. Proclin 300 is a preservative.

2.2.4.3. Assay Procedure:

The micro particle Abbott requires mixing before putting the reagent kit into the system for the first time to suspend micro particles that may have collected during shipping. No additional mixing is necessary after the micro particles have been inserted the first time.

1- For 30 seconds, the micro particle container was inverted.

2- The bottle was examined to confirm that tiny particles were suspended. If the micro particles are still stuck to the container, continue to flip it until the micro particles are entirely suspended.

3-It not use if the micro particles do not suspend; instead, contact your local Abbott representative.

4-After the micro particles were suspended, a septum was attached to the bottle.

5- The architect I system was loaded with the reagent kit.

6-Confirm that all essential reagents were provided.

7-It ensures that septums were clearly visible on all reagent bottles.

8-If calibration was required, it was ordered.

2.2.4.4. Calculation:

To construct a calibration curve, the architect total T3 assay employs a four parameter logistic curve fit data reduction approach (4PLC, Y-weighted).

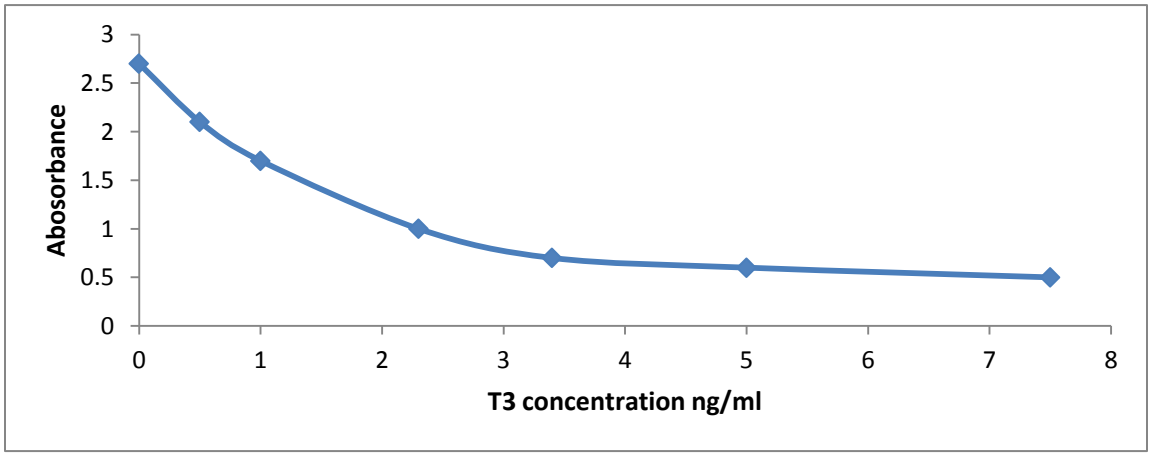

Fig. 2-3 : Standard curve of determination of (T3) hormone concentration

2.2.5. Assessment of Urea Concentration.

Urea concentration was determined by Architect, Abbott laboratories US kit.

2.2.5.1. Principle:

The urea test kit detects the presence of urea in urine, serum, plasma, cell lysates, and tissue homogenates are examples of biological fluids all examples of biological fluids, In a 96-well microtiter plate configuration, samples are compared to a known concentration of urea standard, for 10 minutes, samples and standards are incubated with the urea-hydrolyzing enzyme urease, a chromogenic in alkali solution, to generate a blue-green result. After 30 minutes, the plate is read at an optical density of 580 nm to 630 nm using a conventional 96-well spectrophotometric microplate reader. Higher OD values correspond with higher urea concentrations. The urea concentration of a sample is evaluated by comparing it to recognized urea standards. Up to 50 mg/dL urea, the standard curve is linear.

2.2.5.2. Preparation of Reagents:

Assay buffer 1-1X, Dilute the assay buffer 1:10 with deionized water and well mix. The 1X assay buffer can be stored at 4°C for up to six months.

Ammonia/urease reagent* Reconstitute the urease enzyme in the ammonia reagent solution at 4 mg/ml and well mix until dissolved; for example, add 40 mg of urease 10 ammonia reagent to a 10 MI solution or 100 tests. Make only what you need at the time and discard the urease/ammonia reagent solution.

2.2.5.3. Calculation of Results:

1- The average absorbance and value for each sample, control, and standard were computed.

2. All other standard and sample values, as well as the average zero standard value, were eliminated. This is a change in the background.

3. The absorbance difference was computed for samples with two paired wells with and without urease by subtracting the sample well absorbance values without urease (A-U) from the urease-treated sample well absorbance values (A+U). The (A-U) sample value represents the sample's ammonia background concentration, whereas the (A+U) sample value represents the sample's combined urea and ammonia background concentration. The urea concentration is responsible for the absorbance discrepancy (A).

4. Each sample's absorbance values were compared to the standard curve in order to quantify and estimate the amount of urea present in the sample. Only use values inside the standard curve's range.

(A) = (A + U) - (A-U)

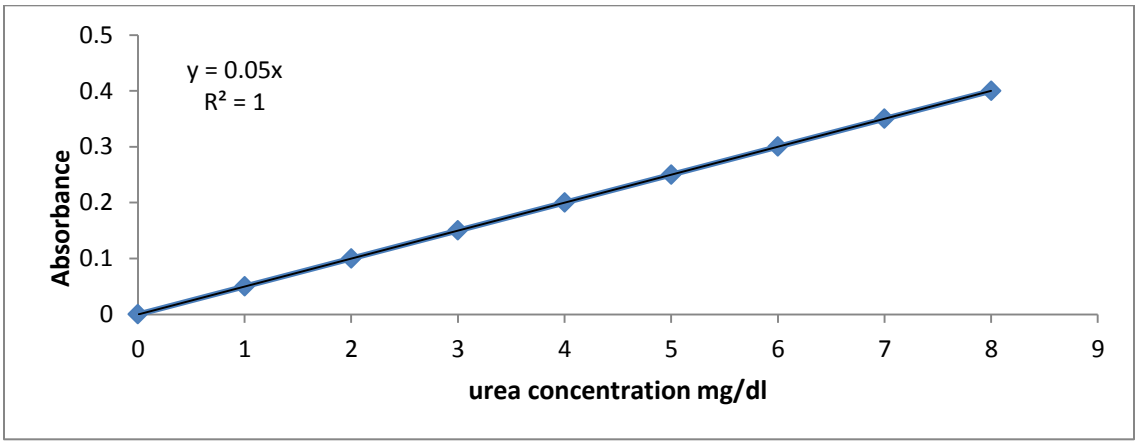

Fig. 2.4 : Standard curve of determination of urea concentration.

2.2.6. Assessment of Creatinine Concentration:

Creatinine concentration was determined by bio system kit.

2.2.6.1. Principle:

The Urinary Creatinine Assay Kit from Cell Biolabs compares creatinine levels in urine samples on a microtiter plate with 96 wells, to a given concentration of creatinine standard samples and standards are incubated for 30 minutes with a reaction reagent that changes color from yellow to brilliant orange when it interacts with creatinine, resulting in the creatinine-picrate complex. A conventional 96-well spectrophotometric microplate reader is used to read the plate at 490 nm. Greater OD levels are linked to higher creatinine levels. The creatinine concentrations in the samples are determined by comparing them to known creatinine standards. The creatinine quencher, which destroys the creatinine-picrate complex and hence removes all creatinine absorbance, can be used to analyze non-specific chromogen interference. The remaining absorbance is caused by non-specific chromogens and can be subtracted from the overall values.

2.2.6.2. Preparation of Reagents:

Creatinine reaction reagent, mix three parts creatinine reaction buffer with one part acid solution, e.g., for 100 experiments, mix 15 mL creatinine reaction buffer with 5 mL acid solution. Thoroughly combine This creatinine reaction reagent can be kept at room temperature for up to a week.

2.2.6.3. Calculation :

1. Each standard and sample's initial average absorbance (Ai) values were computed.

2. The final average absorbance (Af) values for each standard and sample were determined.

3. The corrected absorption (Ac)was calculated by deducting the final absorbance from original absorbance.

4. The absorbance of the creatinine standards was plotted vs the concentration of the creatinine standards to establish the best curve; data can be linearized using log paper or regression analysis software tools.

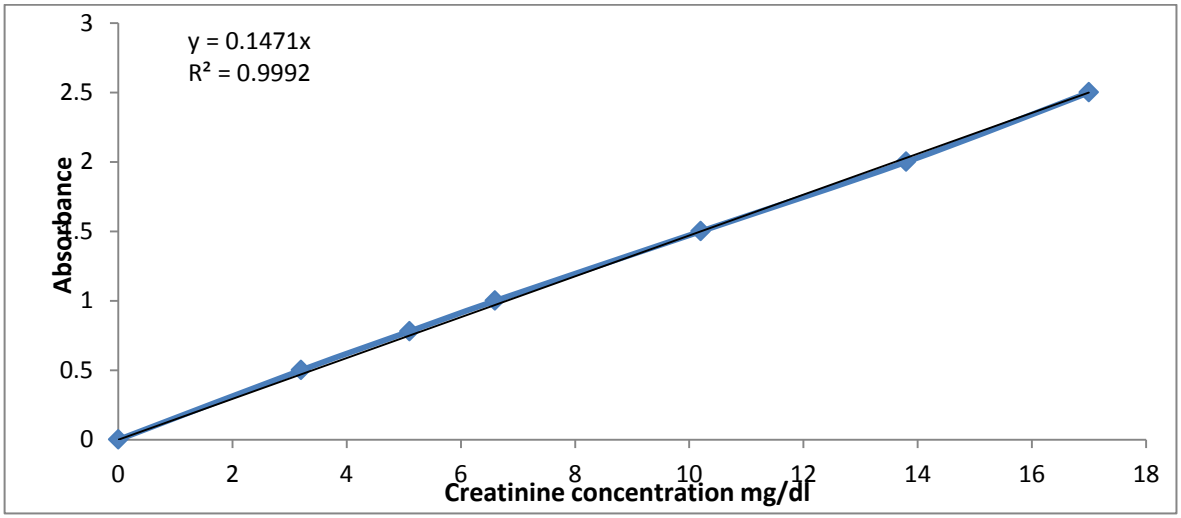

Fig. 2.5: Standard curve of determination of creatinine concentration.

2.2.7 Uric acid

Uric acid concentration was measured using clinical chemistry auto analyzer (Architect plus, C4000, AbbottUSA).

2.2.7.1 Principle

The uric acid test is a two-step process. Uricase oxidizes uric acid to allantion, resulting in the generation peroxide hydrogen (H2O2). H2O2 is produced in the presence of peroxidase (POD) interacts with 4-

aminoantipyrine (4-AAP) and N-(3-sulfopropyl)-3-methoxy-5-methylanaline (HMMPS) to produce a quinoneimine color. The change in absorbance at604 nm that results is proportional to the uric acid content in the sample.

2.2.7.2. Reagents

All reagents are supplied as a liquid, ready to use, two reagent kits:

R1: Ascorbic oxidase and N-(3-sulfopropyl)-3-methoxy-5-methylanaline (HMMPS)

R2: 4-aminoantipyrine (4-AAP), peroxidase and uricase.

2.2.7.3. Procedure

All the assay steps are performed automatically by the instrument.

Normal range 180-420 µmol/L

2.2.8Determination of Total Serum Calcium Concentration

Method:

The method is O-cresolphthalein complexone colorimetric method.

2.2.8.1. Principle:

In an alkaline environment a complex created which has a violet color, resulting from the reaction of O-cresolphthalein complexone (O-CPC) with the ions of calcium.

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.

2.2.8.2. Reagents:

- Calcium standard: Calcium (10 mg/100 mL), or (2.5 mmol/L).

- R1: Reagent 1 (buffer) was the chemical substance (2-amino-2-methyl-propanol) at (10.5) pH, 0.3 mmol/L.

- R2: Reagent 2 the (chromogen) encompassed the compound (O-cresolphthalein complexone 0.16 mmol/L), and (8-hydroxyquinoline 7 mmol/L).

2.2.8.3. 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			**10µL**
Standard		**10µL**	
Reagent 2	**0.5 mL**	**0.5 mL**	**0.5 Ml**
Reagent 1	**0.5 mL**	**0.5 mL**	**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.

2.2.8.4. Calculations:

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

As stated by the equation below, corrected total calcium was gained (289).

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

2.2.8.5. Calculation of Ionized Serum Calcium Concentration

Ionized calcium concentration was obtained as stated by the equation beneath (290).

Ionized calcium in mmol/L =

({[measured calcium in mmol/L×60]-[K/12]})/([60+K])

K' = albumin in (g/L) + [0.19 × total protein in (g/L)].

2.2.9. Determination of Serum Phosphorous Concentration

2.2.9.1. 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.

2.2.9.2. 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.

2.2.9.3. Test 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**	**1.5 Ml**
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.

2.2.9.4. Calculations:

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

2.2.10. Determination of Parathyroid Hormone Levels

PTH level was measured by cobas 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.

2.2.10.1. Test principle

Sandwich principle. Total duration of assay: 18 minutes.

▪ 1st incubation: 50 µL of sample, a biotinylated monoclonal PTH‑specific antibody, and monoclonal PTH‑specific antibody labeled with a ruthenium complex form a sandwich complex.

▪ 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

▪ The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

▪ Results are determined via a calibration curve which is instrumentspecifically generated by 2‑point calibration and a master curve provided via the reagent barcode or e‑barcode.

2.2.10.2. Reagents - working solutions

The reagent rackpack is labeled as PTH.

1- M- Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
2- R1- Anti-PTH-Ab~biotin (gray cap), 1 bottle, 7 mL: Biotinylated monoclonal anti‑PTH antibody (mouse) 2.3 mg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.
3- R2- Anti-PTH-Ab~Ru(bpy) (black cap), 1 bottle, 7 mL: Monoclonal anti‑PTH antibody (mouse) labeled with ruthenium complex 2.0 mg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

2.2.10.3. Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in pg/mL or pmol/L).

Conversion factors: pg/mL x 0.106 = pmol/L

pmol/L x 9.43 = pg/mL

2.3. Statistical analysis

The results were presented as sample size (n), mean ± standard deviation (SD),confidence interval and percentage whenever possible . The statistical significance between the groups was analyzed by Analysis of variance (ANOVA), in addition to Student's t-test were utilized for data assessment. And correlation test between various parameters considering P-value < 0.05 as significant. All statistical significance were done using Microsoft office Excel (2007).

Chapter Three

Results

3. Results

3.1Biochemical Parameter Levels for Patients of Renal Failure

The study included 60 patients divided into 30 patients with acute kidney disease and 30 others with chronic kidney disease in addition to 40 healthy people as a control group, aged 20-60 years. Independent (ANOVA) are used for parameters to compare between studies groups, and the results were expressed by mean± standard deviation (SD) and extraction P-value to show the difference variation

It was observed that the levels of urea, creatinine, uric acid and phosphorous in addition to TSH and PTH were elevated in him compared to the group of AKI and CKD patients with the control group, and a significant difference appeared at p = 0.01, while there was a decrease in the levels of blood calcium and T3 and T4 hormone in him compared to the control group. The group of patients with AKI and CKD with the control group and the appearance of a significant difference p = 0.01 except for T3 hormone, it showed a non-significant difference p = 0.05 as shown in Table 3-1

Table 3-1 Levels of the biochemical parameters of the study subjects for patients of (CKD) and (AKI) group's compare with control group.

Biomarker	Control n=40 Means ± S.D	AKI n=30 Means ± S.D	CKD n=30 Means ± S.D	LSD	P Value
Urea (mmol/L)	4.67 ± 0.48	15.95 ± 5.88	22.33 ± 4.73	2.0314	0.01
Creatnine (mmol/L)	91.05 ± 11.72	297.9 ± 109.54	515.97 ±156.69	51.42	0.01

Uric Acid (umoL/L)	240.65± 29.40	390.03 ± 111.01	341.91 ± 120.58	44.912	0.01
Ca^{2+} (mmol/L)	2.19 ± 0.10	1.96 ±0.18	1.78 ± 0.15	0.0725	0.01
PO_4 (mmol/L)	3.10 ± 0.46	4.05 ± 0.83	5.93 ± 1.93	0.7301	0.01
TSH (µIU/mL	2.04 ±0.71	2.44 ± 1.25	3.42 ± 1.74	0.6193	0.01
T3 (ng/mL)	1.68 ± 0.30	1.50 ± 0.25	1.48 ± 0.22	0.1339	0.05
T4 (ng/mL)	83.43 ± 9.04	80.21 ± 8.55	83.89 ± 7.73	5.5971	0.01
PTH (pg/mL)	36.79 ± 18.43	171..35 ±168.55	491.63 ± 308.91	94.581	0.01

3.2. Effect of Age on Biomarker Levels in Acute Kidney Injury Patients

Independent T-test statistics are used for parameters to compare between studies groups, and the results were expressed by mean± standard deviation (SD) and extraction P-value to show the difference variation.

In this study, acute kidney injury patients were divided into two age groups, the first 20-40 years old and the second 41-69 years old, and comparing them with the control group, where we notice an increase in the levels of urea, creatinine, uric acid and PTH hormone, and the emergence of a significant difference p = 0.01 and a rise in levels TSH hormone and the appearance of a significant difference p = 0.01 for the first age group of AKI patients with it compared with the first age group for the control group, while there was a non-significant difference p = 0.05 when compared to the second age group of AKI patients with the second age group for the control

group There was also a non-significant difference p = 0.05 for high phosphorous levels in him compared to the first age group of the control and there was a significant difference p = 0.01 for his phosphorous levels compared to the second age group of AKI patients with the second age group of the control group.

A decrease in the levels of T3, T4 and calcium hormones was also observed, and a significant difference appeared, p = 0.01 when comparing the first age group of AKI patients with the first age group of the control group. For the control group, except for T4 hormone, it showed a non-significant difference p = 0.0

Table 3-2 The impact of age on the biomarker levels in acute kidney injury patients compare with control.

Biomarker	Patients of AKI	(AKI) Means ± S.D	Control	Control Means ± S.D	LSD	P Value
TSH (µIU/mL)	(20 – 40) y	2.30 ± 1.05	(20 – 40) y	1.71 ± 0.78	1.0095	0.01
	(41 – 69) y	2.62 ± 1.51	(41 – 69) y	2.25 ± 0.59	0.5221	0.05
T3 (ng/mL)	(20 – 40) y	0.48 ± 0.35	(20 – 40) y	1.40 ± 0.85	0.23	0.01
	(41 – 69) y	0.64 ± 0.28	(41 – 69) y	1.37± 0.90	12.037	0.01
T4 (ng/mL)	(20 – 40) y	79.83 ± 14.14	(20 – 40) y	90.80 ± 81.90	8.5846	0.01
	(41 – 69) y	80.71 ± 10.86	(41 – 69) y	84.45 ± 8.55	6.7859	0.05
PTH (pg/mL)	(20 – 40) y	208.91 ± 206.89	(20 – 40) y	38.78 ± 17.51	53.254	0.01
	(41 –69) y	122.22 ± 80.50	(41 – 69) y	35.45 ± 19.27	72.814	0.01
Urea	(20 – 40) y	15.73 ± 7.14	(20 – 40) y	4.43 ± 0.50	2.4196	0.01

(mmol/L)	(41 – 69) y	16.23 ± 3.93	(41 – 69) y	4.84 ± 0.39	2.054	0.01
Creatnine (mmol/L)	(20 – 40) y	278.64 ± 121.47	(20 – 40) y	91.31 ± 12.52	58.75	0.01
	(41 – 69) y	323.23 ± 90.02	(41 – 69) y	90.87 ± 11.43	44.542	0.01
Uric acid (µmoL/L)	(20 – 40) y	404.12 ± 124.52	(20 – 40) y	225.75 ± 27.31	40.803	0.01
	(41 – 69) y	371.62 ± 91.98	(41 – 69) y	250.58 ± 26.86	51.004	0.01
Ca^{2+} (mmol/L)	(20 – 40) y	1.93 ± 0.18	(20 – 40) y	2.21 ± 0.10	0.132	0.01
	(41 – 69) y	1.99 ± 0.18	(41 – 69) y	2.18 ± 0.10	0.088	0.01
PO_4 (mmol/L)	(20 – 40) y	4.29 ± 1.87	(20 – 40) y	2.86 ± 0.42	1.3394	0.05
	(41 – 69) y	3.74 ± 1.80	(41 – 69) y	3.11 ± 0.47	0.6954	0.01

3.3. The Correlation Coefficient of Thyroid and Parathyroid Hormones with Renal Function Tests in AKI Patients

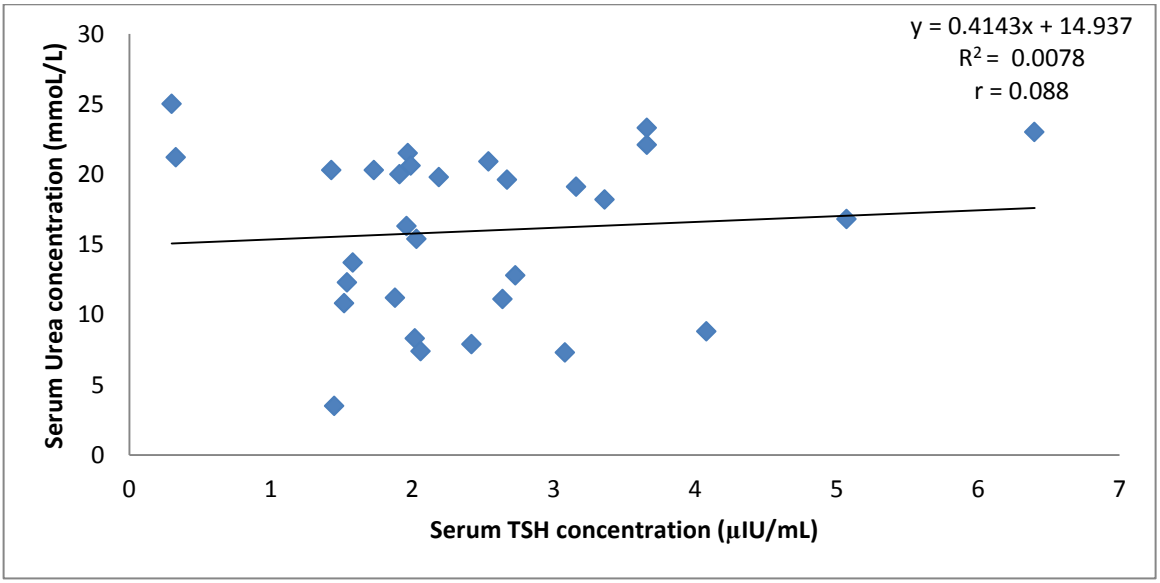

Fig. 3-1: Correlation coefficient of urea concentration and serum TSH concentration in AKI Patients (r = 0.088).

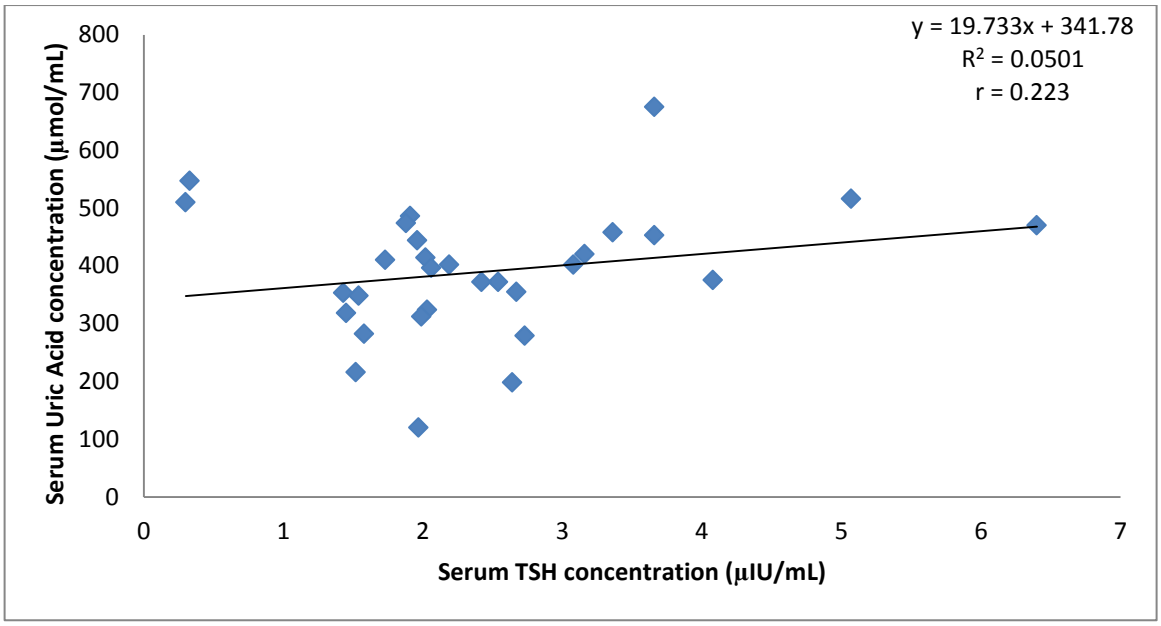

Fig. 3-2 : Correlation coefficient of uric acid concentration and serum TSH concentration in AKI Patients (r = 0.223).

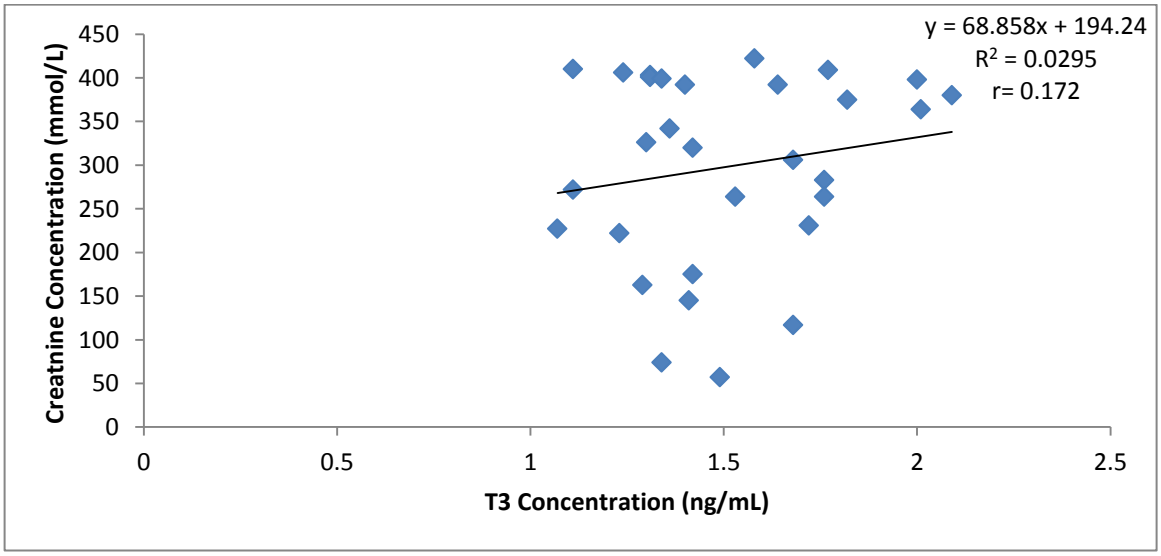

Fig. 3-3: Correlation coefficient of creatnine concentration and serum T3 concentration in AKI Patients (r = 0.172).

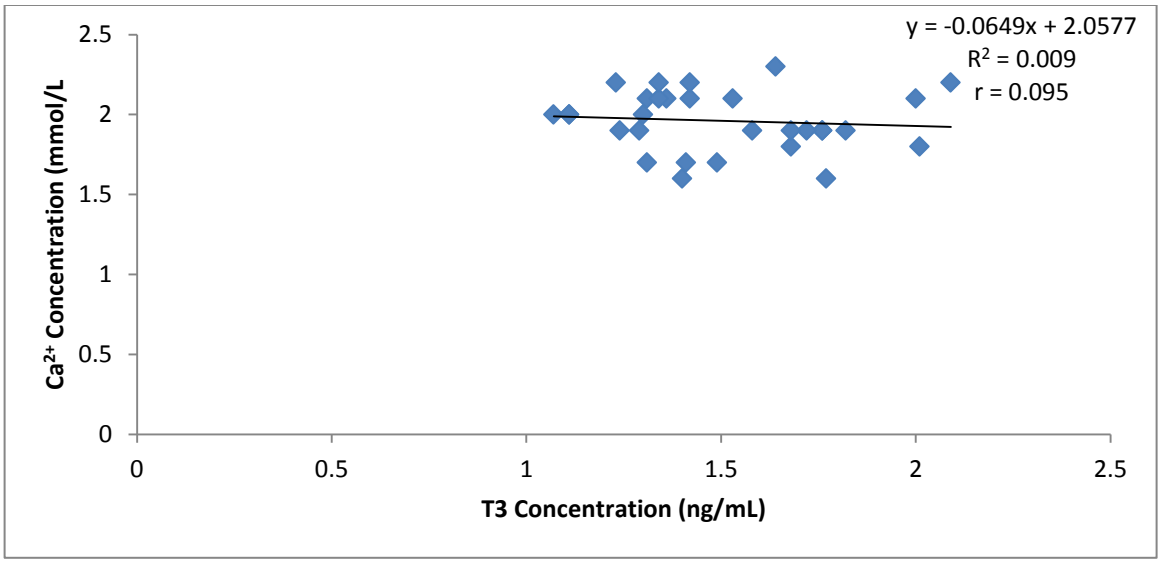

Fig. 3-4 : Correlation coefficient of Ca^{2+} concentration and serum T3 concentration in AKI Patients (r = 0.095).

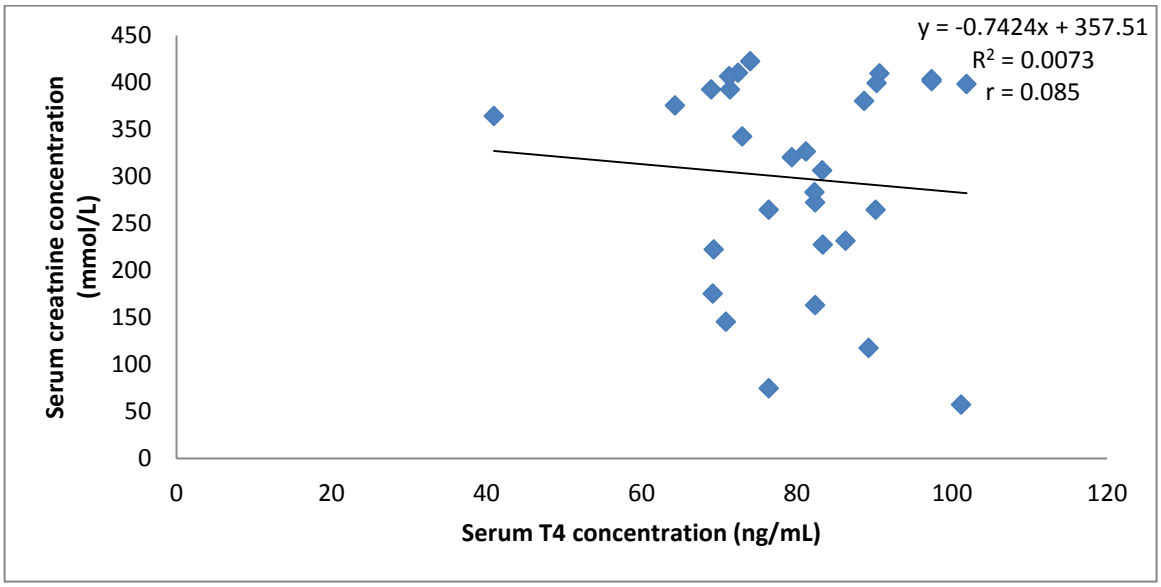

Fig. 3-5 : Correlation coefficient of creatnine concentration and serum T4 concentration in AKI Patients (r = 0.085).

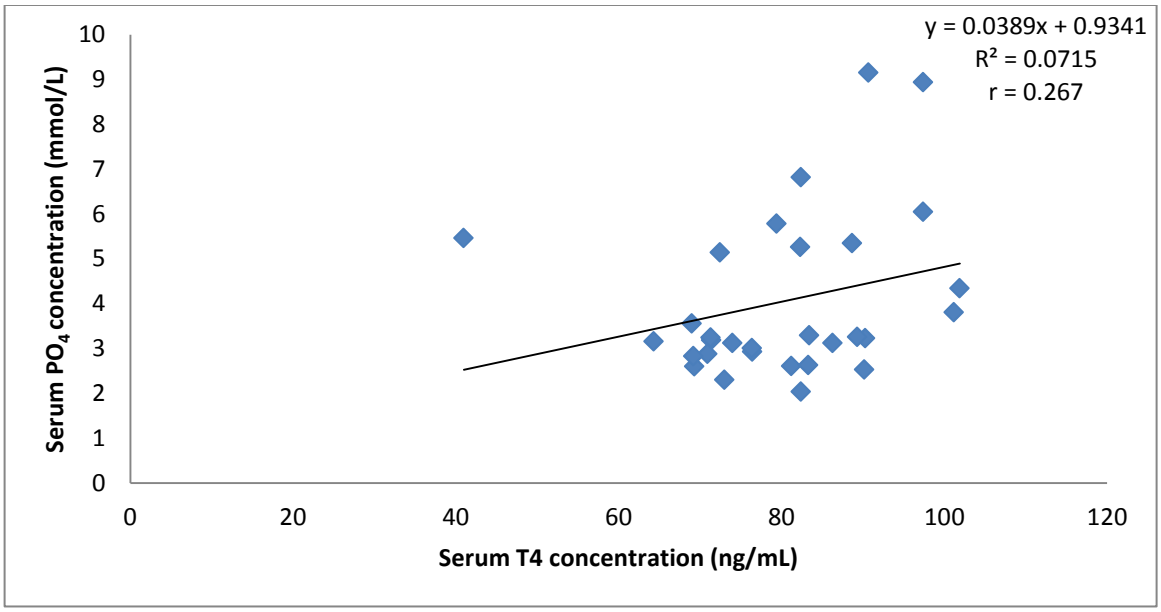

Fig. 3-6 : Correlation coefficient of PO_4 concentration and serum T4 concentration in AKI Patients (r = 0.267).

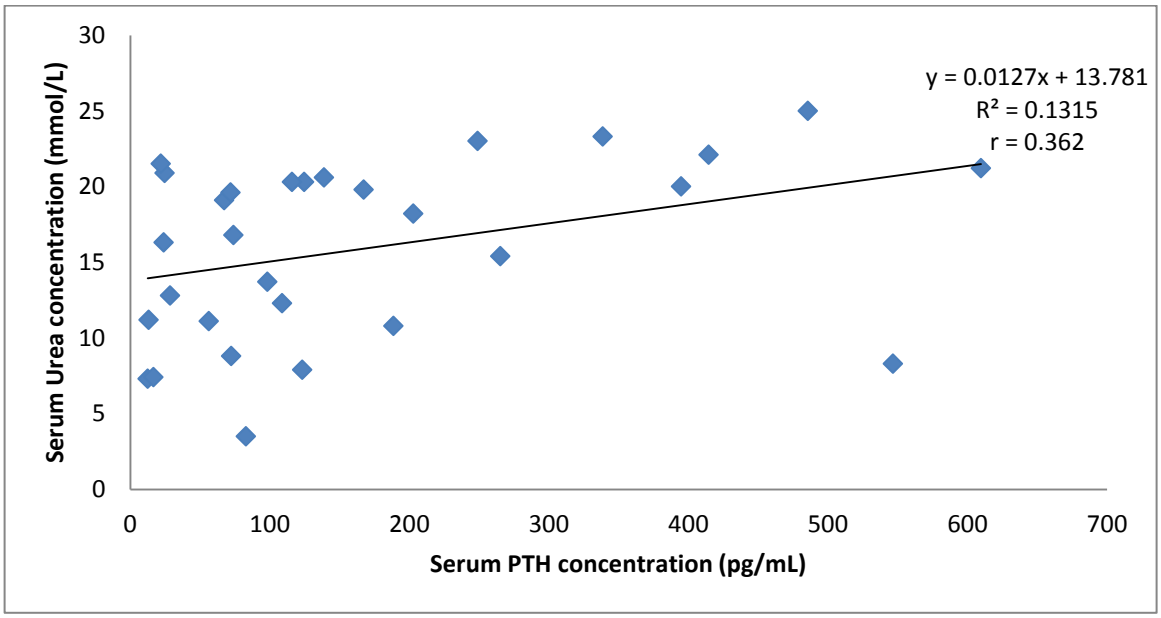

Fig. 3-7 : Correlation coefficient of urea concentration and serum PTH concentration in AKI Patients (r = 0.362).

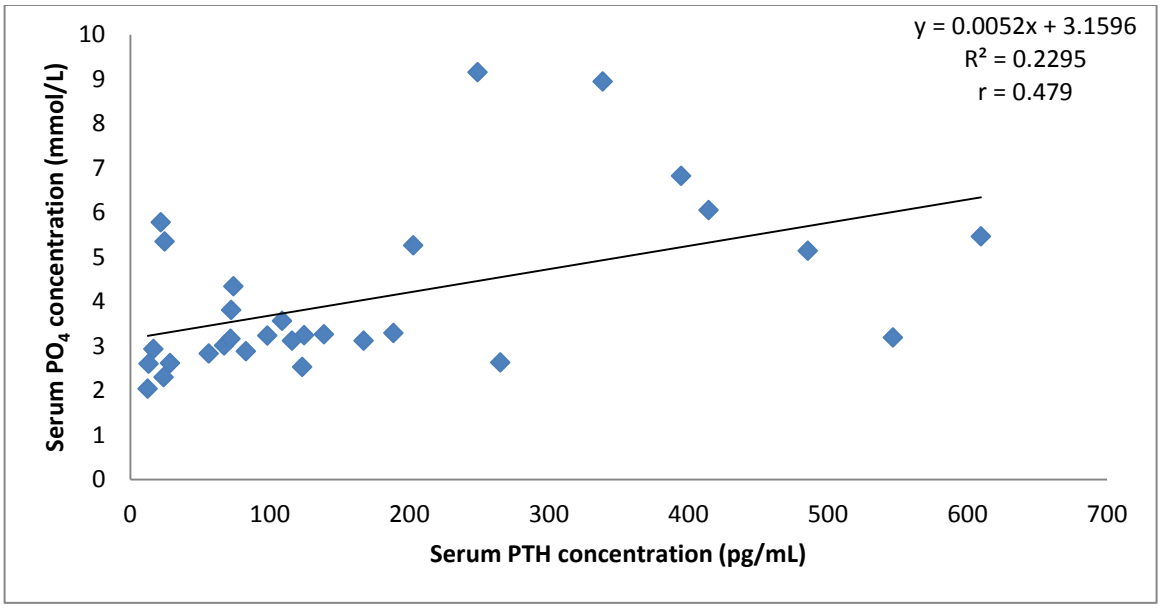

Fig. 3-8 : Correlation coefficient of PO_4 concentration and serum PTH concentration in AKI Patients (r = 0.479).

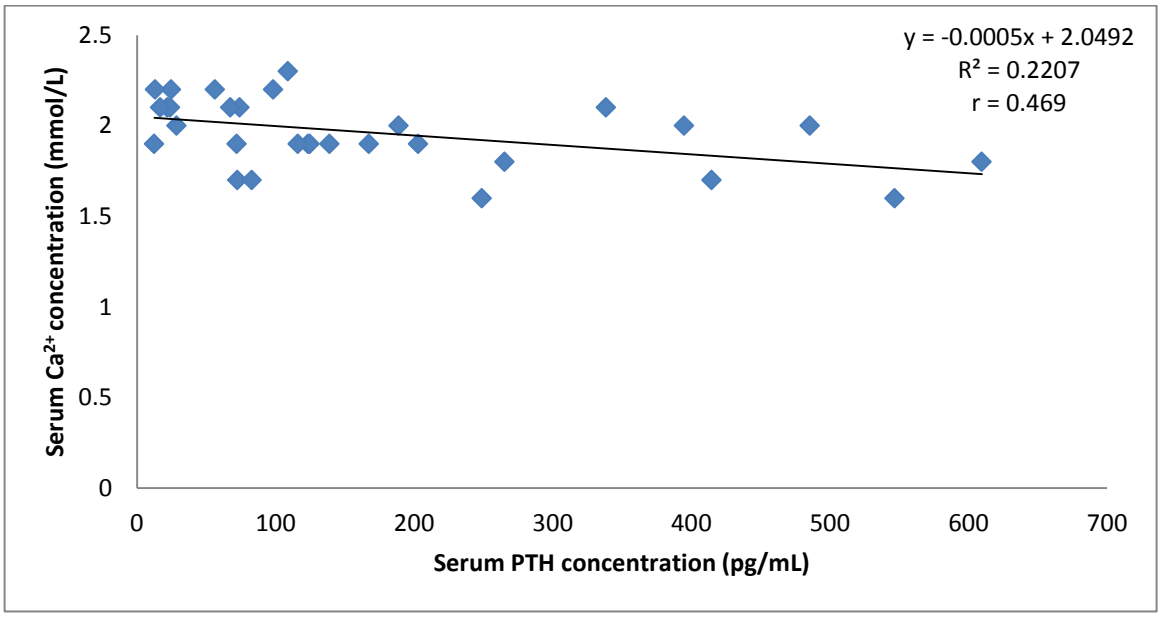

Fig. 3-9 : Correlation coefficient of Ca^{2+} concentration and serum PTH concentration in AKI Patients (r = 0.469).

3.4. Effect of age on Biomarker levels in Chronic kidney Dieses patients

Independent T-test statistics are used for parameters to compare between studies groups, and the results were expressed by mean± standard deviation (SD) and extraction P-value to show the difference variation.

In this study, chronic kidney patients were divided into two age groups, the first 20-40 years old, and the second 41-69 years old, and they were compared with the two age groups of the control group, where an increase in the levels of TSH, PTH, urea, creatinine, uric acid and phosphorous, and the appearance of a difference Significant $p = 0.01$ except for TSH, which showed an insignificant difference $p = 0.05$ when comparing the two age groups of CKD patients with the control group.

A decrease in the levels of T3, T4 and calcium hormones was also observed, and a significant difference appeared, $p = 0.01$ for each of his calcium compared to the two age groups and for T3 hormone when compared to the second age group of CKD patients with the second age group of the control group and his T4 hormone compared to the first age group For CKD patients with the first age group for the control, while there was a non-significant difference $p = 0.05$ for T3 hormone for the first age group and T4 hormone for the second age group for CKD patients compared with the control group.

Table 3-3 relation of age on the Biomarker levels in Chronic kidney Disease patients compare with control group.

Biomarker	Patients of CKD	(CKD) S.D ± Means	Control	Control S.D ± Means	LSD	P Value
TSH (µIU/mL)	(20 – 40) y	3.37 ± 1.11	(20 – 40) y	2.78 ± 1.71	0.8072	0.05
	(41 – 69) y	3.43 ± 1.95	(41 – 69) y	3.25 ± 0.59	0.8409	0.05
T3 (ng/mL)	(20 – 40) y	0.27 ± 0.20	(20 – 40) y	1.40 ± 0.24	0.2309	0.05
	(41 – 69) y	0.36 ± 0.32	(41 – 69) y	1.37 ± 0.20	0.196	0.01
T4 (ng/mL)	(20 – 40) y	80.19 ± 16.52	(20 – 40) y	90.81± 81.90	11.089	0.01
	(41 – 69) y	81.60 ± 10.84	(41 – 69) y	84.45 ± 8.55	5.7776	0.05
PTH (pg/mL)	(20 – 40) y	618.1 ± 427.20	(20 – 40) y	38.78 ± 17.51	216.79	0.01
	(41 – 69) y	445.6 ± 250.26	(41 – 69) y	35.45 ± 19.27	103.18	0.01
Urea (mmol/L)	(20 – 40) y	21.55 ± 4.16	(20 – 40) y	4.43 ± 0.50	2.1417	0.01
	(41 – 69) y	22.61 ± 4.98	(41 – 69) y	4.84 ± 0.39	2.054	0.01
Creatnine (mmol/L)	(20 – 40) y	465.00 ± 141.28	(20 – 40) y	91.31 ± 12.52	72.167	0.01
	(41 –69) y	534.50 ± 160.95	(41 – 69) y	90.87 ± 11.43	66.327	0.01
Uric acid (µmoL/L)	(20 – 40) y	312.94 ± 62.46	(20 – 40) y	225.75 ± 27.31	37.567	0.01
	(41 – 69) y	352.45 ± 135.43	(41 – 69) y	250.58 ± 26.86	56.845	0.01
Ca^{2+} (mmol/L)	(20 – 40) y	1.70 ± 0.20	(20 – 40) y	2.21 ± 0.10	0.1295	0.01
	(41 – 69) y	1.80 ± 0.12	(41 – 69) y	2.18 ± 0.10	0.0678	0.01
PO_4 (mmol/L)	(20 – 40) y	6.32 ± 2.10	(20 – 40) y	2.86 ± 0.42	1.1133	0.01
	(41 – 69) y	5.79 ± 1.89	(41 – 69) y	3.11 ± 0.47	0.8064	0.01

3.5. Correlation coefficient between biomarkers parameters in patients of CKD.

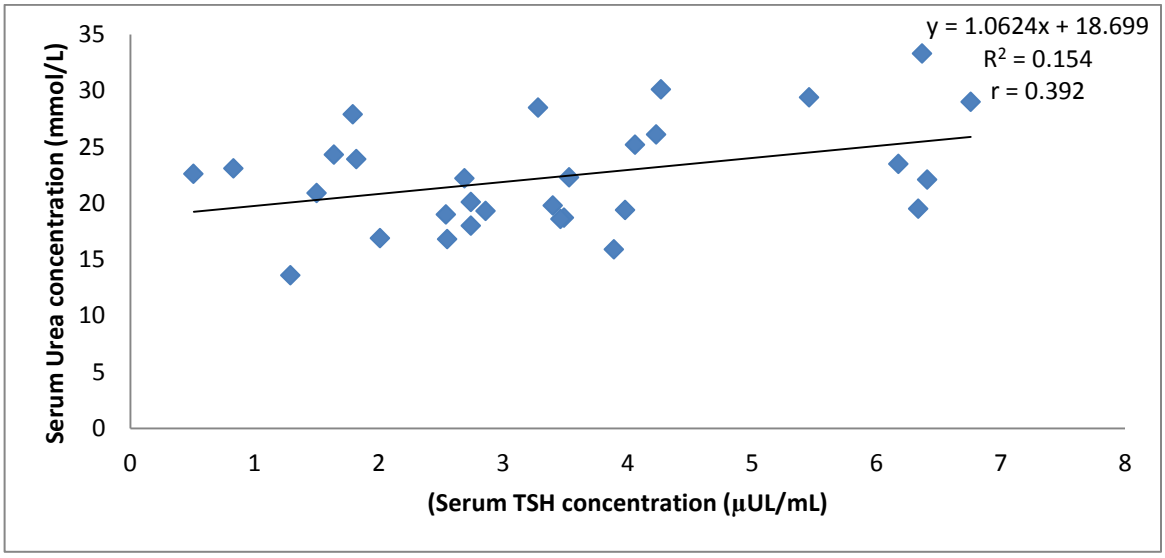

Fig. 3-10 : Correlation coefficient of urea concentration and serum TSH concentration in CKD Patients (r = 0.392).

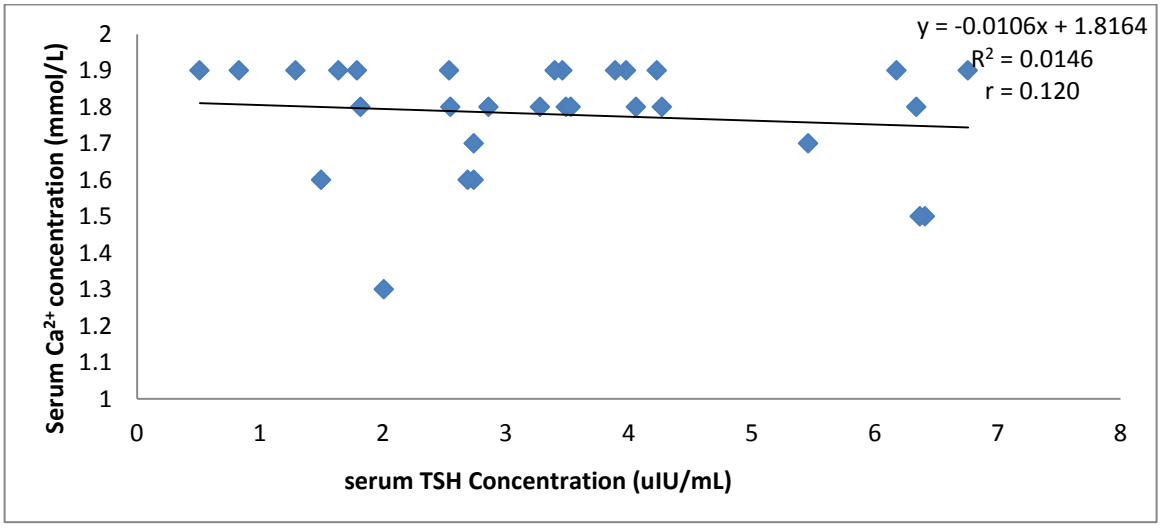

Fig. 3-11 : Correlation coefficient of Ca^{2+} concentration and serum TSH concentration in CKD Patients (r = 0.120).

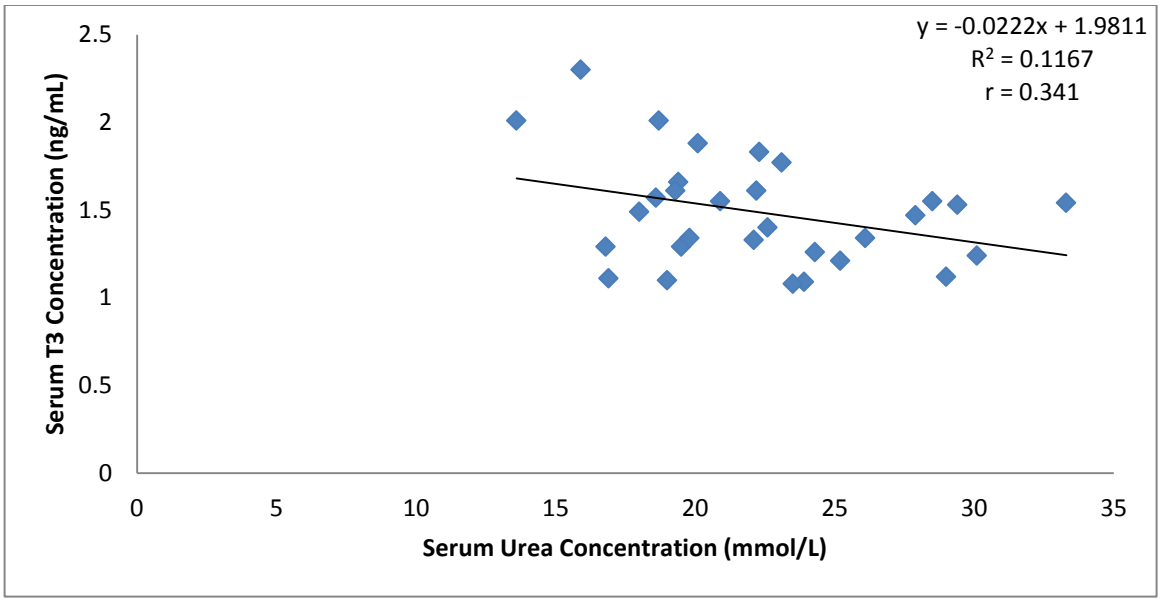

Fig. 3-12 : Correlation coefficient of urea concentration and serum T3 concentration in CKD Patients (r = 0.341).

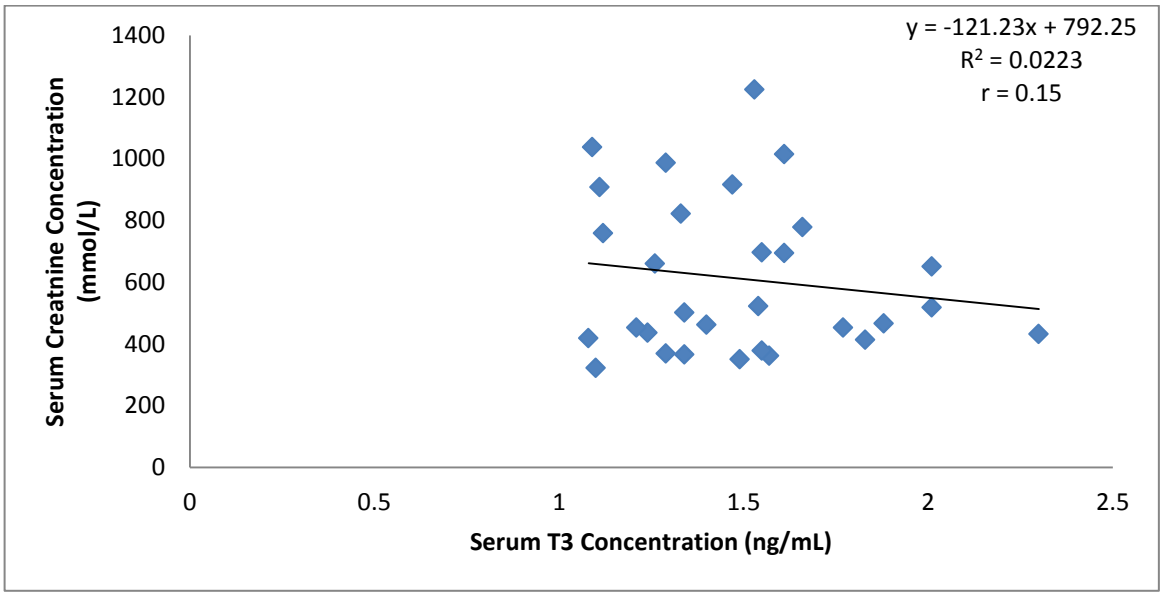

Fig. 3-13 : Correlation coefficient of creatnine concentration and serum T3 concentration in CKD Patients (r = 0.15).

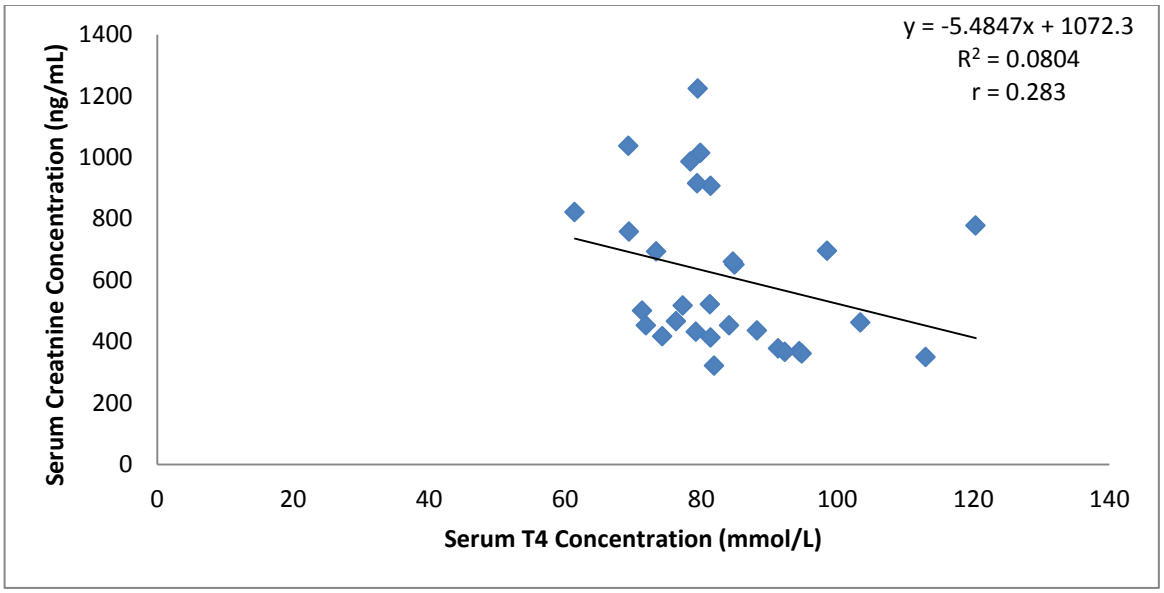

Fig. 3-14 : Correlation coefficient of creatnine concentration and serum T4 concentration in CKD Patients (r = 0.24).

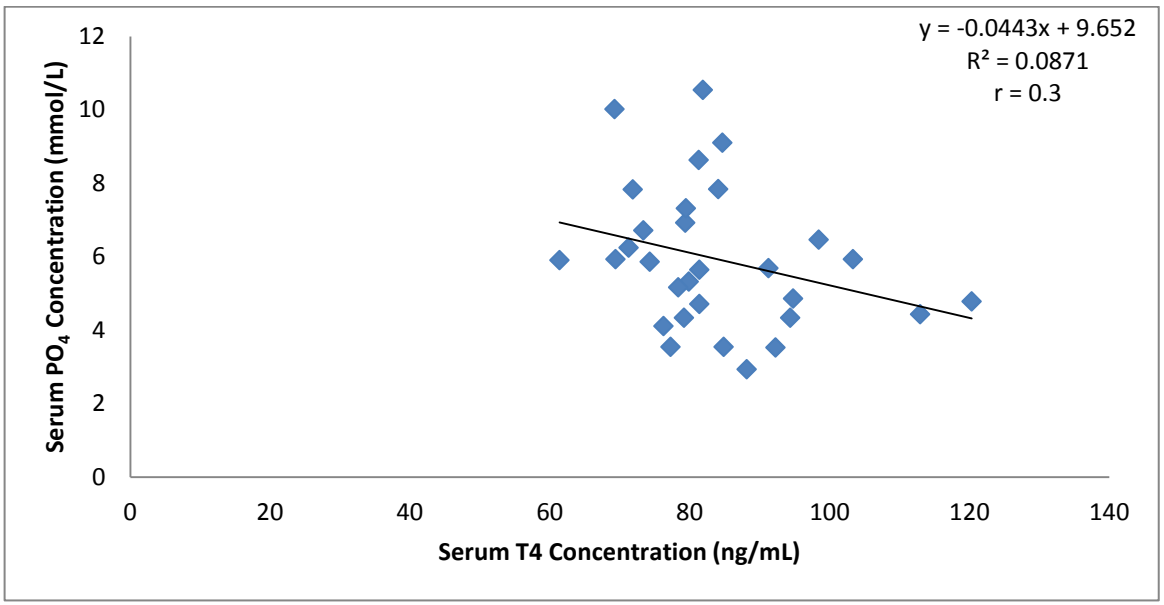

Fig. 3-15 : Correlation coefficient of PO_4 concentration and serum T4 concentration in CKD patents (r = 0.3).

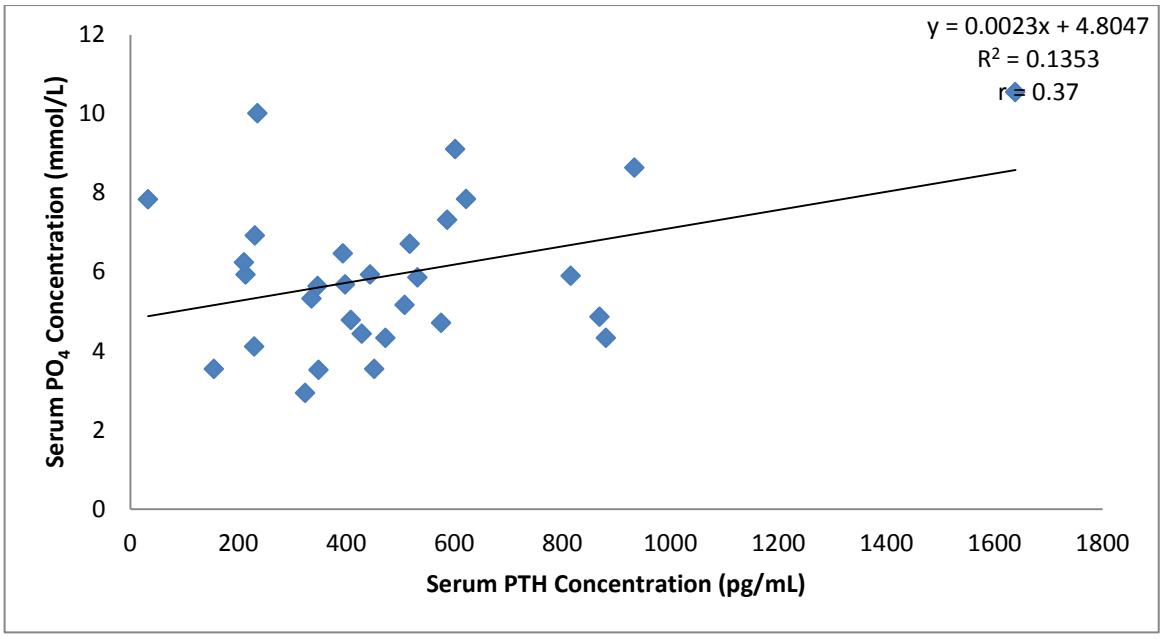

Fig. 3-16 : Correlation coefficient of PO_4 concentration and serum PTH concentration in CKD patents (r = 0.37).

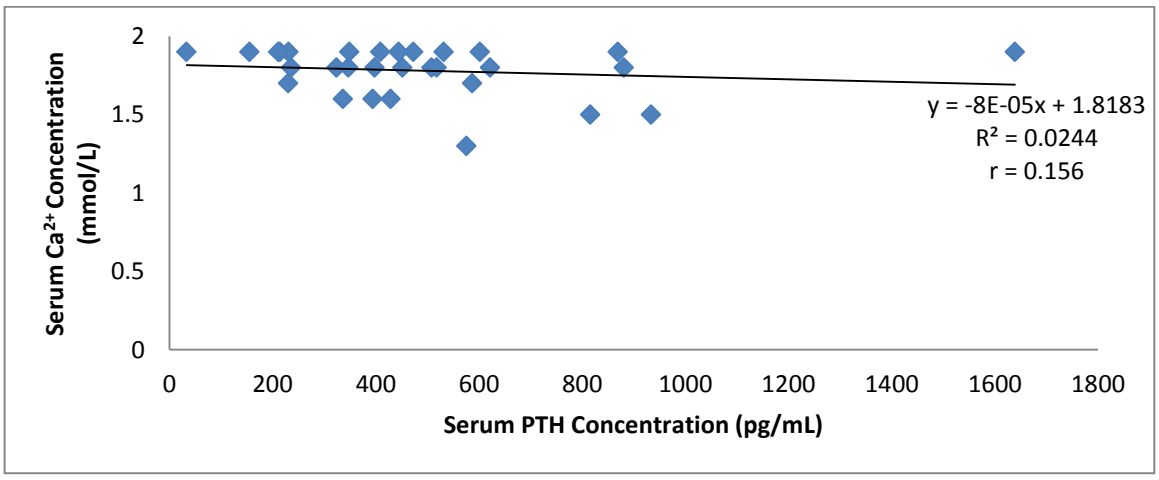

Fig. 3-17 : Correlation coefficient of Ca^{2+} concentration and serum PTH concentration in CKD patents (r = 0.156).

3.6. Effect of the Body Mass Index on Biomarker Levels in Acute Kidney Injury Patients

In this study, BMI was divided into three groups: normal weight, overweight, and severely obese

1- Normal weight BMI= 18.5 - 24.9

2- Overweight BMI= 25 – 29.9

3- Severely obese BMI= > 35

Fig. 3-18 Shows the difference of urea levels in three groups of BMI in patients of AKI it illustrated the high level in severely obese group

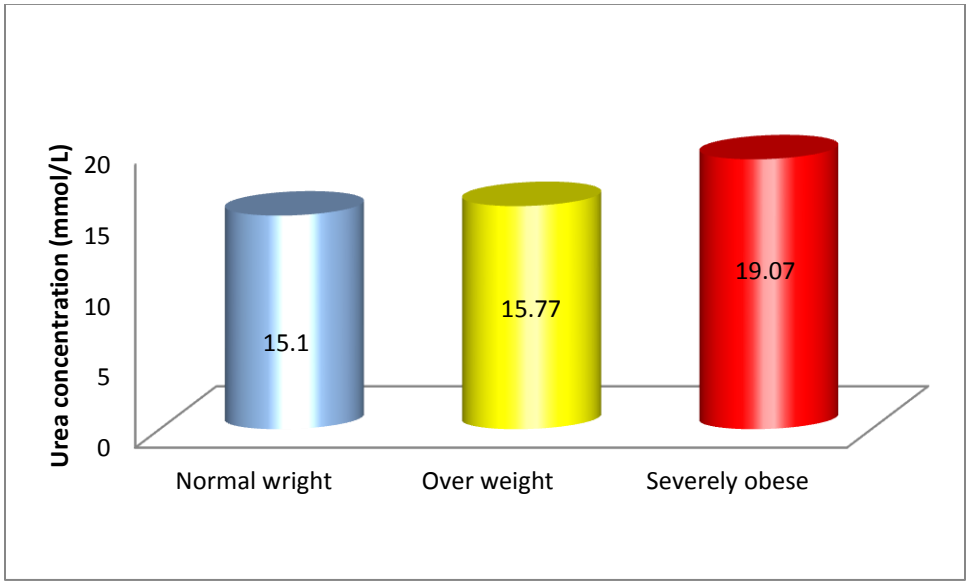

Fig. 3-18 : Relationship between urea concentrations with BMI groups

Fig. 3-19 Shows the difference of calcium levels in three groups of BMI in patients of AKI it illustrated the high level in severely obese group.

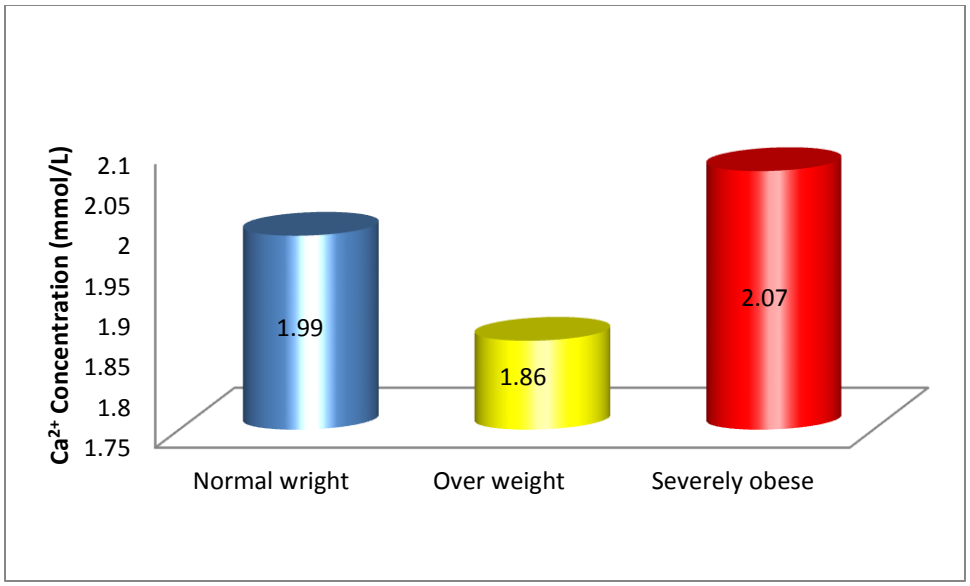

Fig. 3-19 Relationship between calcium concentrations with BMI groups

Fig.3-20 Shows the difference of phosphorus levels in three groups of BMI in patients of AKI it illustrated the high level in severely obese group.

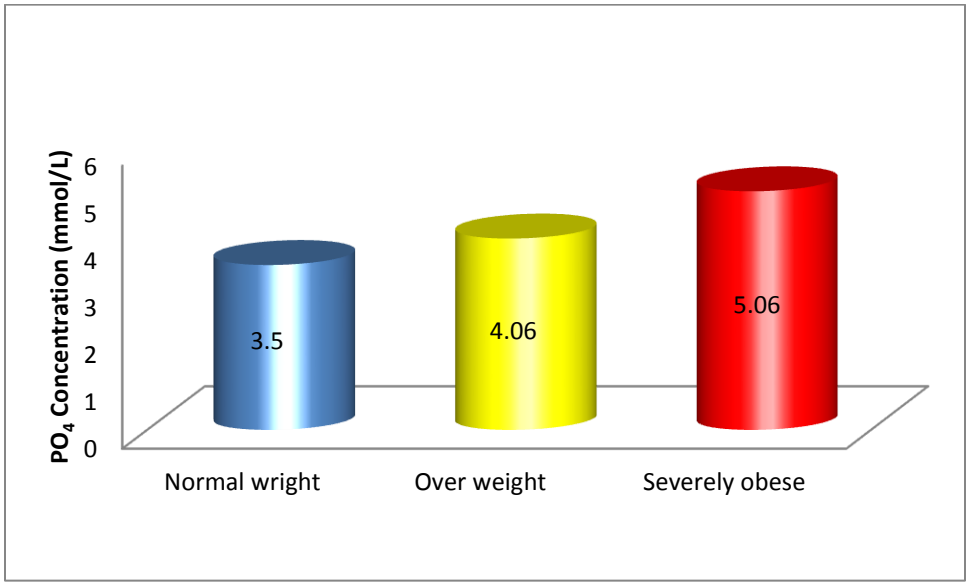

Fig. 3-20 : Relationship between PO_4 concentrations with BMI groups

Fig. 3-21 Shows the difference of TSH levels in three groups of BMI in patients of AKI it illustrated the high level in severely obese group.

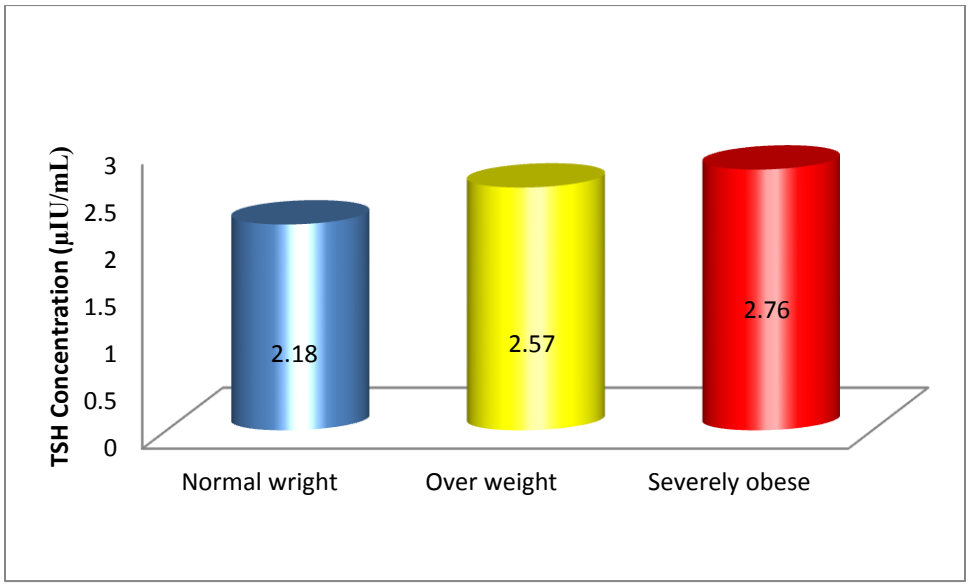

Fig. 3- 21: Relationship between TSH concentrations with BMI groups

Fig. 3-22 Shows the difference of T3 levels in three groups of BMI in patients of AKI it illustrated the high level in severely obese group.

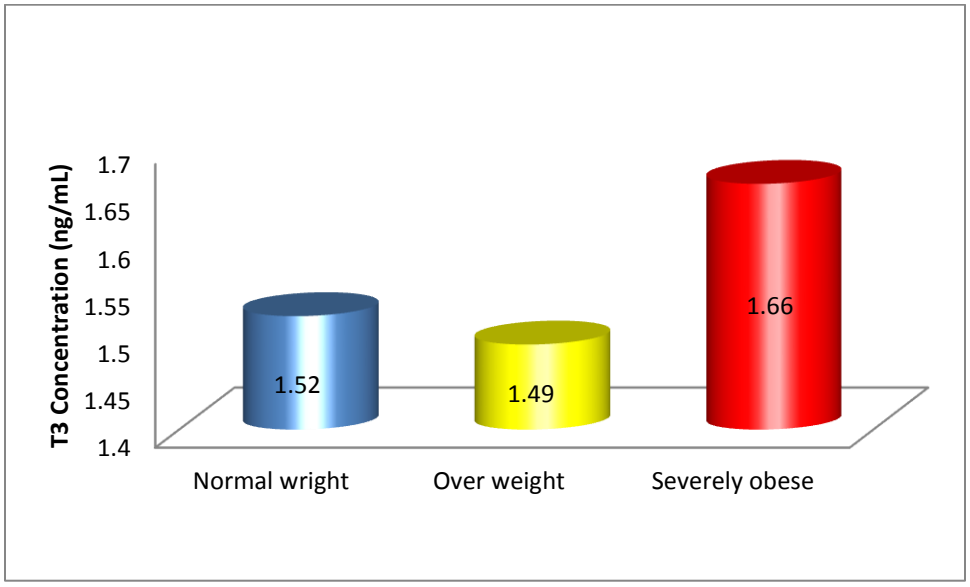

Fig. 3-22 : Relationship between T3 concentrations with BMI groups

Fig.3-23 Shows the difference of T4 levels in three groups of BMI in patients of AKI it illustrated the high level in severely obese group.

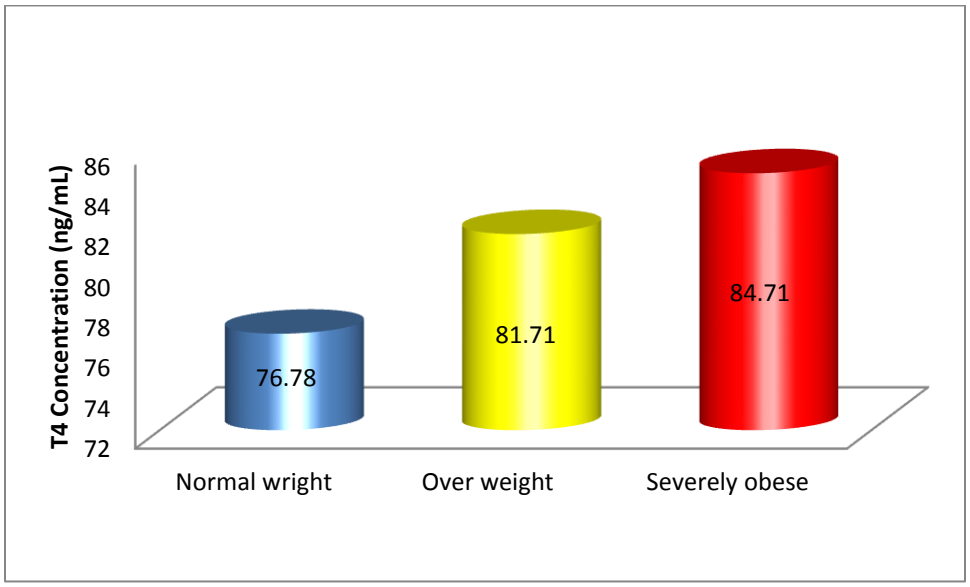

Fig. 3-23 Relationship between T4 concentrations with BMI groups

Fig.3-24 Shows the difference of PTH levels in three groups of BMI in patients of AKI it illustrated the high level in overweight group.

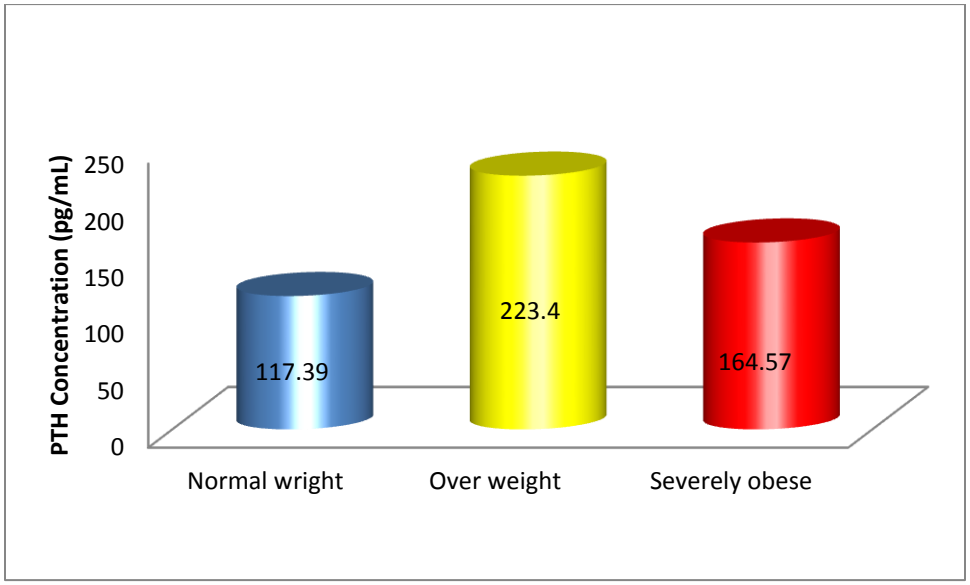

Fig. 3-24 : Relationship between PTH concentrations with BMI groups

3.7. Effect of Body Mass Index on the Biomarker Levels in Chronic Kidney Disease

The results of effect of BMI on the levels of biomarkers parameters were illustrated . Figure 3-25 showed elevated of urea concentrations in patients of CKD with obese weight.

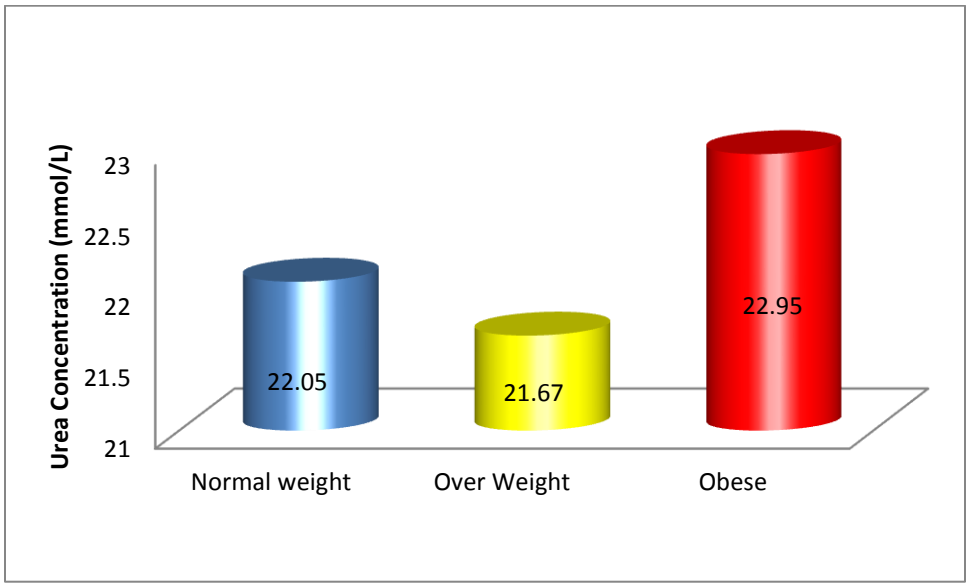

Fig. 3-25 : Relationship between urea concentrations with BMI groups

Fig. 3-26 Show the difference of creatnine levels in three groups of BMI in patients of CKD it illustrated the high level in obese group.

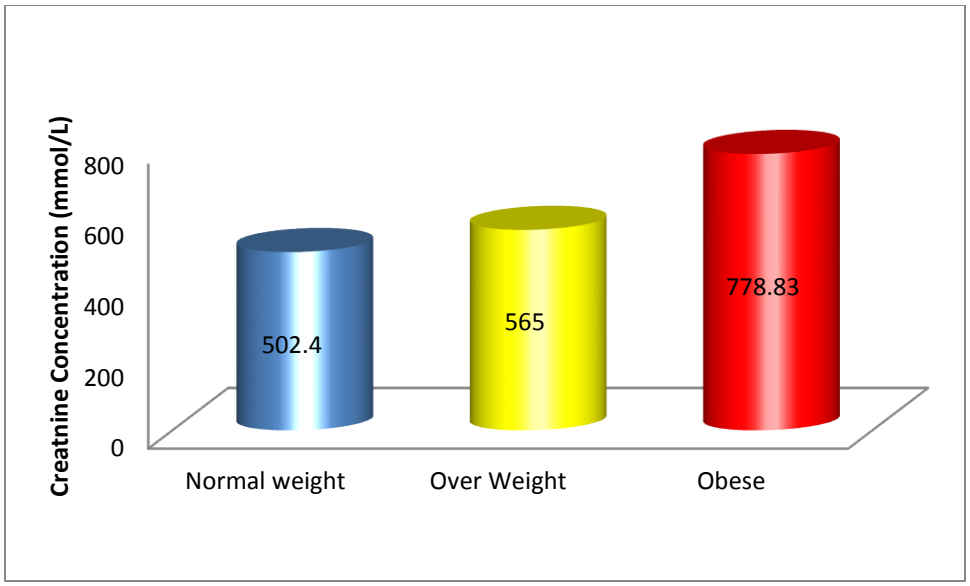

Fig. 3-26 : Relationship between creatnine concentrations with BMI groups

Fig.3-27 Shows the difference of calcium levels in three groups of BMI in patients of CKD it illustrated the high level in overweight group.

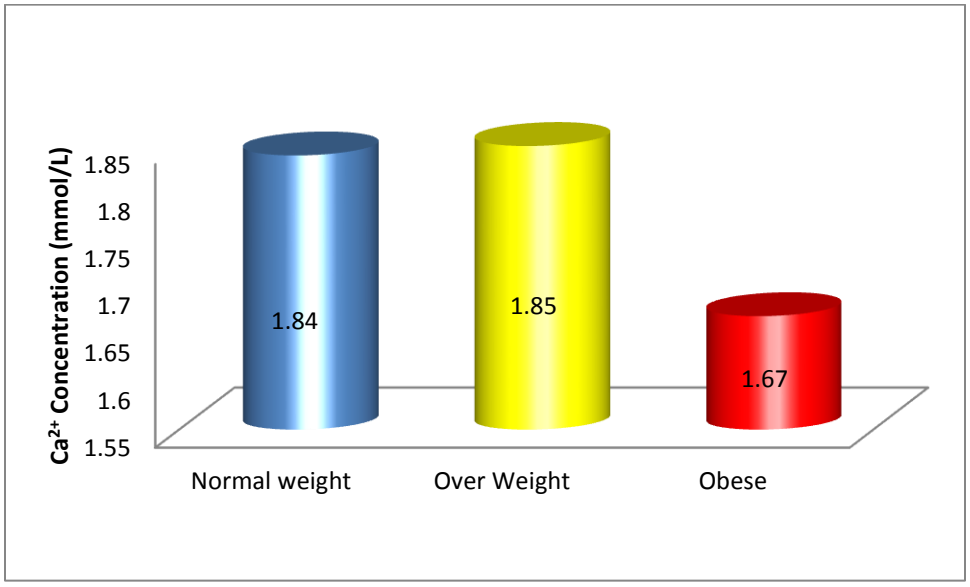

Fig. 3-27 : Relationship between calcium concentrations with BMI groups

Fig.3-28 Shows the difference of phosphorus levels in three groups of BMI in patients of CKD it illustrated the high level in obese group

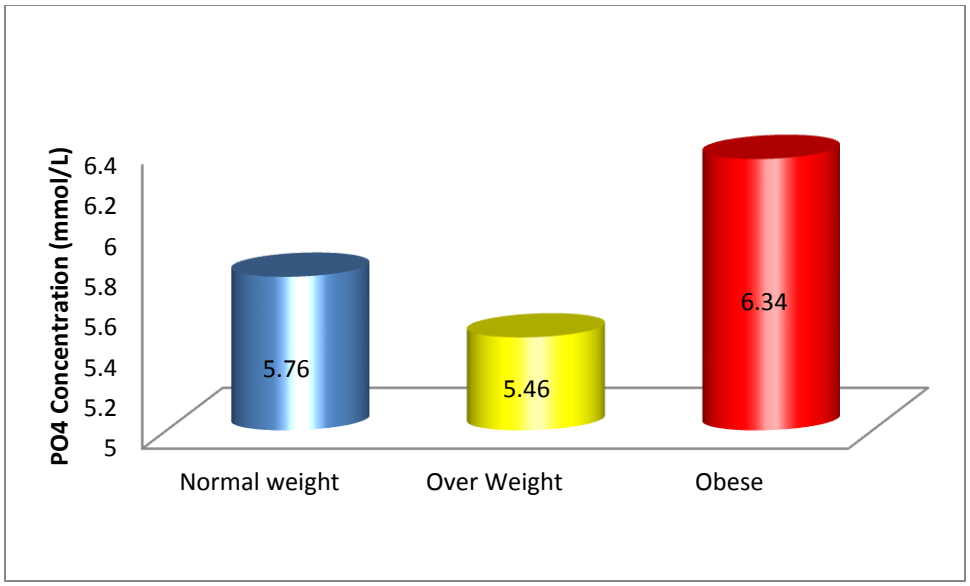

Fig. 3-28 : Relationship between phosphorus concentrations with BMI groups

Fig.3-29 Shows the difference of T3 levels in three groups of BMI in patients of CKD it illustrated the high level in overweight group.

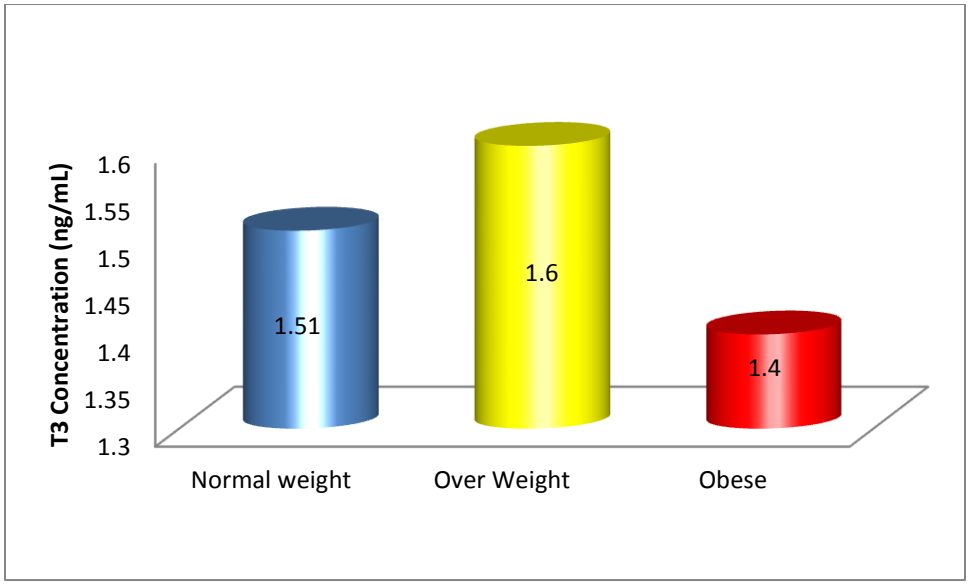

Fig. 3-29 : Relationship between T3 concentrations with BMI groups

Fig.3-30 Shows the difference of T4 levels in three groups of BMI in patients of CKD it illustrated the high level in overweight group.

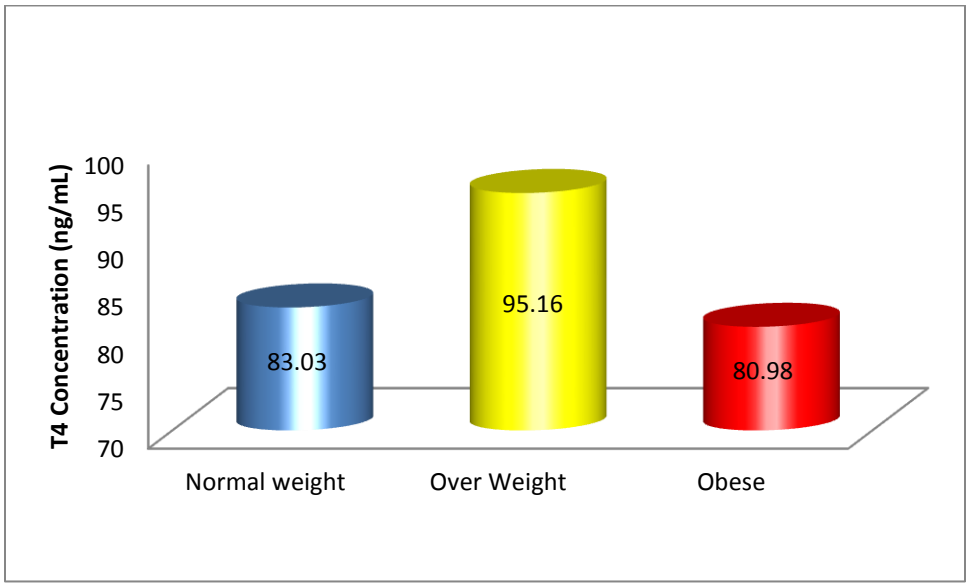

Fig. 3-30 : Relationship between T4 concentrations with BMI groups

Fig.3-31 Shows the difference of PTH levels in three groups of BMI in patients of CKD it illustrated the high level in obese group

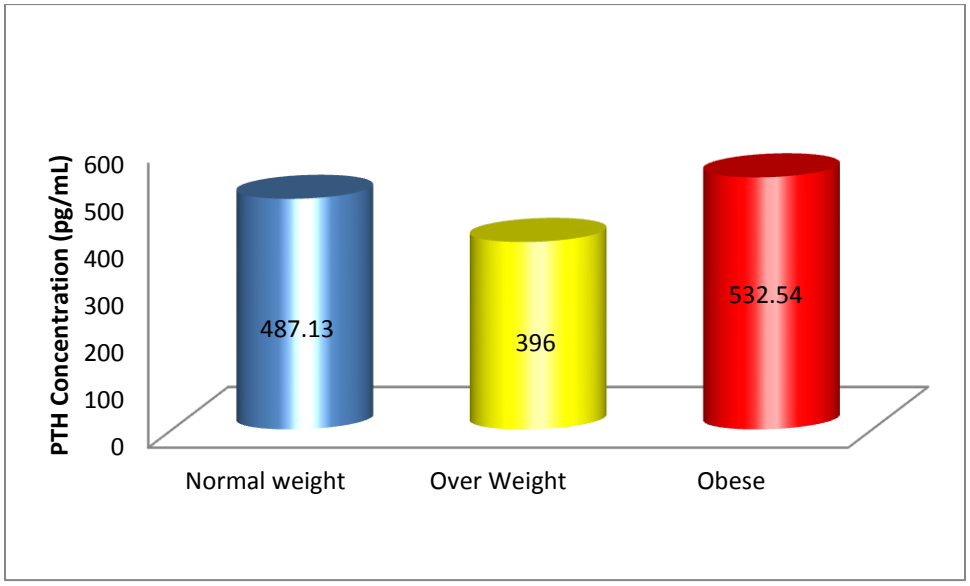

Fig. 3-31 : Relationship between PTH concentrations with BMI groups

3.8. Relation between Duration of Illness with Biomarker in Patients

Divide the duration of AKI patients into three groups, the first group from (1 to 4) weeks, the second group from (5 to 8) weeks, and the third group from 9 to 34) weeks with regard to calcium, phosphorous, TSH and (T3 concentrations as shown in the figure (3-32) And the concentrations of urea, creatinine, T4 and PTH as shown in the figure (3-33)

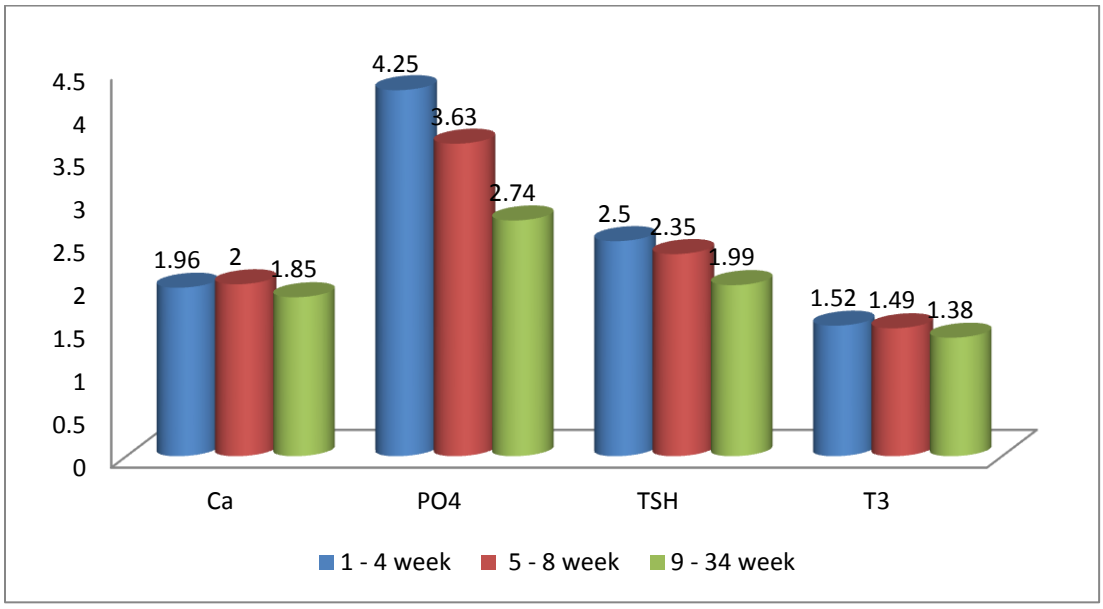

Fig. 3-32 : The relationship between duration and concentration of calcium, phosphorous, TSH, and T3 for AKI patients

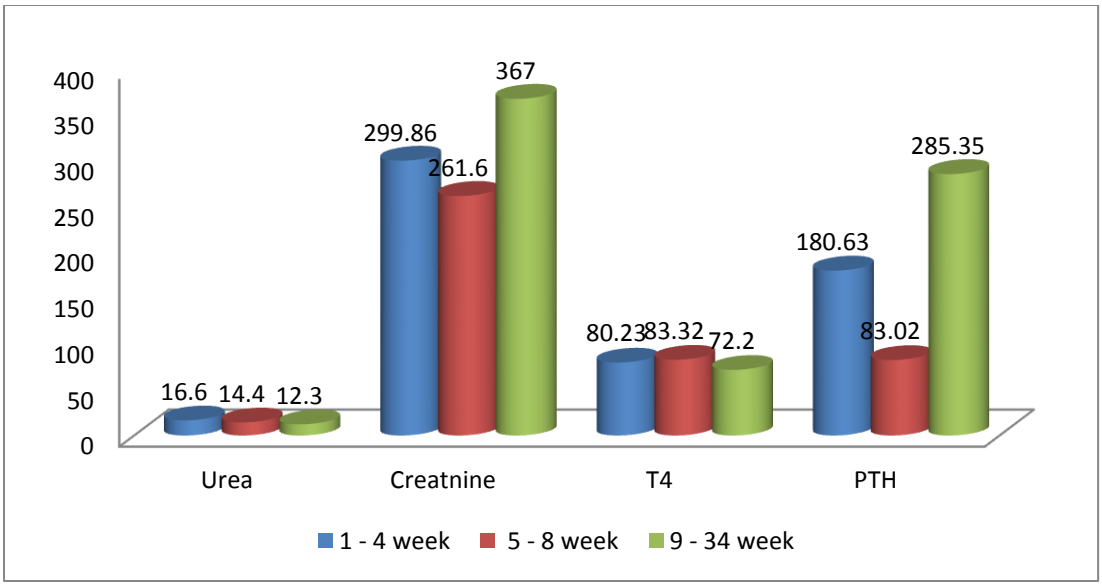

Fig. 3-33 : The relationship between duration and concentration of Urea, Creatnine, T4, and PTH for AKI patients

The duration of CKD patients was divided into three groups, the first group from(2 to 12) months, the second group from (13 to 38) months, and the third group from (39 to 52) months for calcium, phosphorous, TSH, and T3 concentrations as shown in the figure (3-34) and the urea and T4 concentrations. and PTH as shown in the figure(3-35)

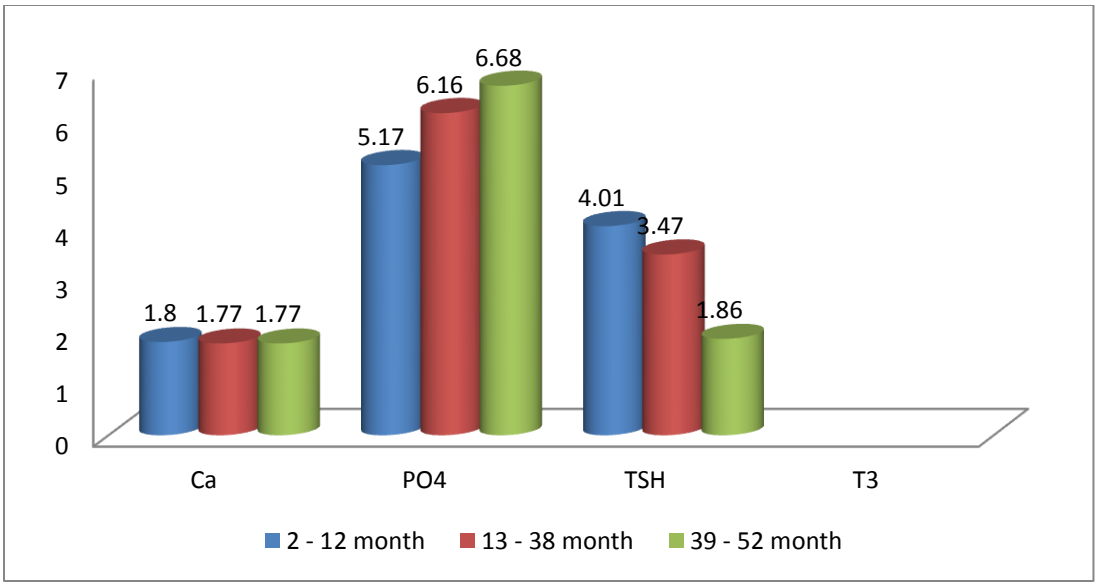

Fig. 3-34 : The relationship between duration and concentration of calcium, phosphorous, TSH, and T3 for CKD patients

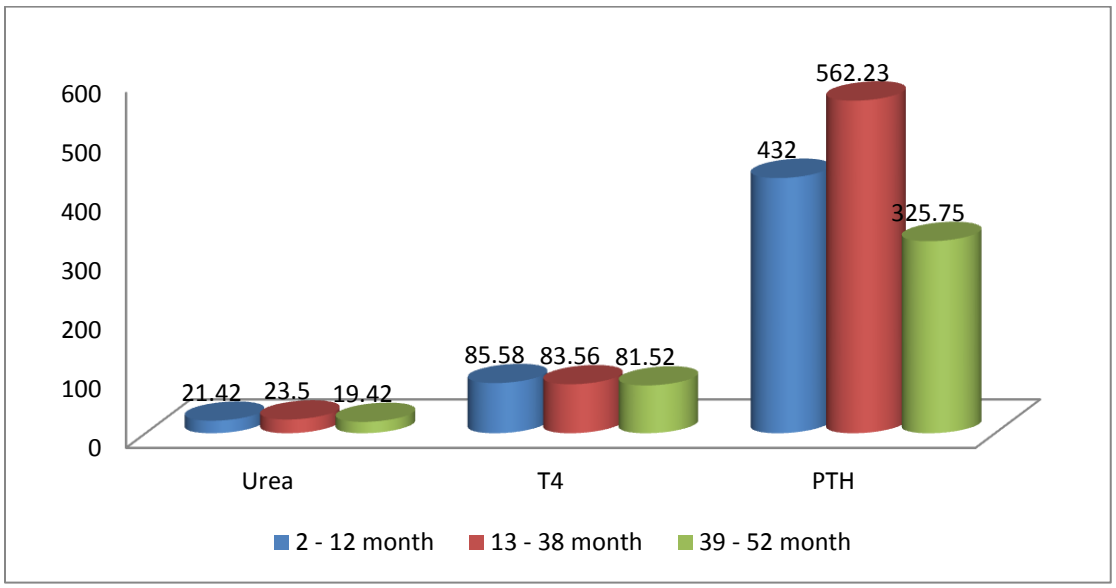

Fig. 3-35 : The relationship between duration and concentration of Urea, T4, and PTH for CKD patients

Chapter Four

Discussion

4. Discussion

4.1. Relation between Thyroid Hormones and Kidney Failure

Patients with renal failure especially CKD may be at a higher risk for thyroid dysfunction due to a variety of factors including iodine retention, metabolic acidosis, mineral deficiency (e.g. selenium), protein loss, changes in the regulation of the hypothalamic-pituitary-thyroid axis, and changes in thyroid hormone metabolism, degradation, and excretion [106].

According to the present study's findings, there was a significant increase $p = 0.01$ ($P < 0.05$) in the average blood urea level in the AKI and CKD group compared to the control group, as demonstrated in Table (3-1).

Most patients with kidney failure suffer from high levels of urea as a result of fluid retention in the body when the kidneys are damaged or not working properly [104].

The current study's findings revealed a considerable rise in creatinine levels in the AKI and CKD groups as compared to the control group in Table 3-1.

This significant increase in creatinine levels is caused by impaired renal function and the kidney inability to eliminate toxins and nitrogenous waste. The findings of this study corroborate those of another study, with Abdelmula M.A ;Botoual S.E. and Gud Allah M, They found the creatinien levels were increased patients of renal disease with hypothyroidism [105].

The results of present study revealed a significant increase, ($p = 0.01$) of the levels of TSH hormone in the AKI and CKD group compared with the control group in Table 3-1.

Most patients with kidney failure, especially end-stage kidney disease, suffer from hypothyroidism, This study showed that kidney failure patients, especially those undergoing dialysis, have low levels of thyroid hormone and high TSH [106].

This finding clearly indicates that more severe CKD will be associated with more complications [107], including thyroid disorders, which was consistent with the results demonstrated by many epidemiological and cross-sectional studies [108], In the largest U.S.-based study by Lo *et al* [109], observed a high prevalence of hypothyroidism with incrementally lower categories of eGFR among the Third National Health and Nutrition Examination Survey [110,111].

The results of the current study showed significant decreased of the levels of T3 hormone in the AKI and CKD group compared to the control group in Table 3-1.

Most patients with renal failure, especially those undergoing dialysis, have Low T3 levels may also be due to the decreased peripheral (extra thyroidal) conversion from T4 to T3 due to decreased clearance of the inflammatory cytokines [112]. This study are agree with a study by Sting *et al* [113].

The current study shows lower significant levels of T4 hormone in the AKI and CKD group compared to the control group in Table 3-1.

Various patterns of thyroid profile modification in CKD patients have been documented in the literature. Singh *et al*. investigated thyroid hormone levels and oxidative stress in 40 patients with renal failure and 35 controls, They discovered a substantial drop in T3, T4 levels in individuals with renal failure compared to controls [114], this is line with the current study's findings.

The results in Table 3-1, showed a high significantly of PTH levels for the AKI and CKD groups when compared with control group.

The increase in PTH levels observed in renal failure patients undergoing dialysis treatment in this study is related to the occurrence of hyperparathyroidism which is pathophysiological mainly due to hyperphosphatemia and hypocalcemia as reported in our results [115].

The results showed an increase in phosphorous levels and a Calcium levels in the AKI and CKD groups were lower than in the control group in Table (3-1).

Somerville and Kaye were discovered that an elevation in serum phosphorus generated skeletal resistance to PTH's calcemic impact uremic rats [116]. In rats treated with either acute or chronic renal failure, Massry *et al*. found that calcitriol treatment substantially restored resistance to PTH's calcemic effect [117], therefore, it is consistent with the results of the current study.

4.2. Effect of Age on Biomarker Levels in Acute Kidney Injury Patients

Although acute renal insufficiency can occur even in normal individuals, it increases in elderly people [118], Elderly AKI patients are less likely to restore renal function [119], the diagnostic criteria for AKI are based on changes in GFR, which are usually estimated as the kidneys filter fluid and eliminate waste products. Nitrogenous ones, including urea, creatinine, and others [120].

The results of the current study showed a significant difference in urea and creatinine levels for the first age group of AKI patients (20-40) years compared to the first age group of the control group. In addition to the appearance of a significant difference for the second age group of AKI patients (41-69) years when compared to the second age group of healthy people (control group), as shown in Table 3-2.

SCr levels, however, are regulated not only by GFR but also by creatinine production rate, tubular secretion, and distribution volume [121], SCr is also impacted by nonrenal variables such as muscle mass, diet, illness, and drugs, all of which are age-related [122], Whereas creatinine clearance is an important marker for the estimation of GFR [120].

The increase in urea and creatinine levels of AKI patients in this study is identical to the study conducted, Beier et al. [123] and Feinfeld *et al* [124].

The results of the current study showed a significant difference in uric acid levels for the first age group of AKI patients (20-40) years compared to the first age group of the control group. In addition to the appearance of a

significant difference for the second age group of AKI patients (41-69) years when compared to the second age group of healthy people (control group), as shown in Table 3-2.

Uric acid has recently been revived as a possible mediator of AKI, [125,126], with the idea that this ancient biological component is driving inflammatory pathways that may exacerbate acute kidney injury [127,128].

Indeed, uric acid is no longer thought to be physiologically inactive [129], but rather to have a variety of effects, including being a pro- and anti-oxidant [130], a neurostimulant, an inducer of inflammation, and an activator of the innate immune response [131], Uric acid's actions may explain why it is linked to the development of chronic renal disease Especially in the elderly [132], as well as hypertension, coronary artery disease, metabolic syndrome, and diabetes [133].

Experimentally, significant hyperuricemia with AKI has been demonstrated to produce AKI with a simultaneous reduction in glomerular filtration rate (GFR) and renal blood flow (RBF) [134,135], It is in agreement with the results of his study et Johnson al in (2013) [136,137].

The results of the current study showed a significant difference in his TSH levels in comparison to first age group of AKI patients with the first age group for control

But it showed an insignificant differencefor the second age group of AKI patients with the second age group for the control group as shown in the Table 3-2.

Most of the AKI patients in this study were suffering from hypothyroidism, where we notice higher levels of TSH in them compared to healthy people [138], hypothyroidism is often associated with age, the levels of TSH in elderly people are higher than in younger people. A community survey in the United Kingdom showed Increased risk of hypothyroidism for individuals over 55 years of age, especially AKI patients, and this is in line with the findings of this investigation.

The present data indicated an association between TSH and urea r = 0.088 as shown in Figure 3-1, Our findings agreed with those of Vaneet Kaur *et al* [139]. and Vandana Saini *et al* [140], Which also showed an association between urea and TSH.

The present data indicated an association between TSH and uric acid r = 0.223 as shown in Figure (3-2), Giordano *et al* [141], discovered a 33.3 % prevalence of hyperuricemia in hypothyroid individuals. Erickson et al. [142], and Dariyerli *et al*. [143], did similar research and discovered there is an association between urea and TSH.

The results of the current study showed a significant difference in the levels of T3 and T4, comparing the first age group of AKI patients with the first age group for control, as well as the appearance of a significant difference for T3 hormone, comparing the second age group of AKI patients with the second age group of the control group, while T4 showed a non-significant difference as shown in the Table 3-2.

Thyroid hormones are known to affect kidney function. Hypothyroidism may lead to alterations in renal blood flow and glomerular filtration rate (GFR),and renal tubular function. It is known that the

concentration of nitrogenous waste and creatinine in the blood increases in case of hypothyroidism [144], and it decreases after giving the hormone thyroxine, and this is more evident in the elderly, Where we notice a decrease in T3, T4 concentrations for AKI patients who suffer from hypothyroidism, it is consistent with the results of the study conducted by Cevher *et al* in (2016) [145].

The present data indicated a positive correlation between T3 hormone and creatinine r = (0.172) as shown in figure 3-3, The results of previous studies showed a positive correlation between T3 hormone and creatinine, it is consistent with the studies conducted by Attaullah, Haq, and Ahmed *et al* in (2015) [146].

The present data indicated a negative correlation between T4 hormone and creatinine, r = (0.085), as shown in figure 3-5, it is consistent with the studies conducted by Mooraki *at e*l in (2003) [147], Dragović at el in (2012) [148], and Stojanoski *at el* in (2011) [149].

The outcomes of the current study showed a correlation between thyroid hormones T3, T4, phosphorous and blood calcium as shown in figure 3-4 and 3-6.

Hypothyroidism leads to impaired resorption or mobilization of calcium in the bones, which leads to a decrease in calcium in the blood. Increased production of calcitonin, which enhances tubular phosphate absorption and favors tubular secretion of calcium, leads to hypocalcemia and hyperphosphatemia as appears in hypothyroidism [150], Our findings were consistent with those of Abbas MM *et al* [151], Alcalde *et al* [152], and Schwarz C *et al* [153].

The results of this study showed a significant difference in PTH levels for AKI patients of the first age group compared to the first age group of the control group. While was a non-significant difference for the second age group of AKI patients with the second age group for the control group, as shown in the Table 3-2.

In this cross-sectional case series, patients with AKI who had elevated levels of PTH had hyperparathyroidism compared to the control group among AKI patients, high levels of phosphorous in the blood compared to healthy people [154], which is often associated with the severity of hyperphosphatemia, which is believed to be caused by increased secretion of bone cells and not due to decreased renal clearance [155]. Most of the AKI patients were suffering from calcium deficiency due to irregular metabolism of minerals Where hyperparathyroidism stimulates the bones to release bone calcium in to blood [156], so most patients suffer from bone pain and osteoporosis, and the elderly AKI patients increase more than the younger ones. In healthy people, which is shown in Table 3-2. Therefore, it is consistent with the results of the study conducted by Shrestha *at el* in (2004) [157].

The present data indicated a strong correlation between PTH and calcium r = (0.469) in figure 3-9. Also, there is an association with phosphorous, (r = 0.479) in figure 3-8, In addition to the existence of a correlation between parathyroid hormone and urea (r = 0.362) in figure 3-7, It is consistent with the results of the study conducted by Natoli *et al*(2013) [158], Palmer *et al* (2015) [159], Centeno *et al* (2019) [160].

4.3.Effect of Age on Biomarker Levels in Chronic Kidney Disease Patients

With age, the incidence and prevalence of diseases such as diabetes, high blood pressure and chronic kidney disease increases rapidly [161], according to national registry data [162], The percentage of 60-year-olds in the population with ESRD has been steadily increasing worldwide [163,164].

In this study, we divided CKD patients into two age groups and compared them with the first and second age groups of the control group, where the results of the study showed a non-significant difference for TSH in them, comparing the first age group of CKD patients with the first age group of the control group, Also, a non-significant difference appeared for the second age group of CKD patients with the second age group for the control group, in the Table 3-3.

Hypothyroidism is an increase in TSH in the blood. It is not a rare condition. According to research, the frequency of hypothyroidism in adults ranges from 4 to 10%, and it increases with age, particularly in females over the age of 45 [165].

Furthermore, earlier researches showed a close relationship between CKD patients and hypothyroidism [166], the prevalence of CKD was high in patients with hypothyroidism and more frequently [167].

Data from (14,623) adult participants from the third national survey in the United States revealed that the prevalence of hypothyroidism increased with decreased GFR and an increase in serum creatinine and urea concentrations [168,169].

And it is identical to the results of this study, where CKD patients of both age groups were suffering from an increase in the levels of urea, creatinine and uric acid, and a significant difference appeared in it compared to the two age groups of the control group, in Table 3-3.

The correlation of TSH was weak with urea concentration (r = 0.392) as shown in figure 3-10, It is consistent with the results of the study conducted by Biondi and Cooper et al in (2008) [140], Åsvold et al in (2011) [108].

The results of the current study showed an non-significant difference for T3 hormone and a significant difference for T4 hormone for the first age group of CKD patients, with the first age group of control as well as the appearance of a significant difference for T3 hormone compared to the second age group of the control group and non-significant difference for T4 hormone for the second age group of CKD patients compared to the second age group of the control group, in Table 3-3.

Singh *et al*. examined thyroid hormone levels and oxidative stress in 40 people with renal failure and 35 healthy people. They discovered a substantial drop in T3, T4 levels in individuals with renal failure compared to controls [114].

Haria and Lunia et al. did a research, To assess the state of thyroid hormones in patients with CKD, they discovered lower total thyroid hormone and T3 levels in 74% of CKD patients, but TSH and T4 levels were comparable to controls [113].

They also found an important negative correlation between urea, serum creatinine and T3, T4 hormones [170].

In this study, there was a negative correlation between T3 and urea (r = 0.341) and creatinine (r = 0.15), as shown in figure 3-12, 3-13.

In addition to a negative correlation between T4 and creatinine (r = 0.283) as shown in Figure (3-14)

These results were approach with other studies in Srivastava et al in (2018) [171].

The present study's findings revealed a significant difference for his PTH hormone, comparing the two age groups of CKD patients with the two age groups of the healthy group, Table 3-3.

Hyperparathyroidism is one of the main complications of CKD patients [172], which is responsible for damage to the skeleton and blood vessels with an increased risk of bone fractures and mortality due to changes in mineral metabolism such as hyperphosphatemia [173,174], low vitamin D activity and hypocalcemia [175], and increases with progression. Age, especially for patients over the age of 60 [176], and especially for those undergoing dialysis [177,178,179].

Hyperparathyroidism has often been associated with fibrous osteitis [180], which is characterized by increased bone turnover, with cortical osteoporosis, fractures, and osteoporosis [181], The results of previous studies confirm the increased incidence of bone fractures among CKD patients, especially among the elderly, compared to those younger than 40 years old Sprague *et al* in (2016) [182], Wagner *et al* in (2014) [183].

Hyperparathyroidism leads to an increase in the concentration of phosphate and a decrease in blood calcium due to the high rate of uncontrolled bone turnover that leads to osteoporosis and calcifications in the kidneys and blood vessels [184].

The results of this study showed a significant difference in the levels of calcium and phosphorous in them compared to the healthy group, in Table 3-3.

The results of this study showed a positive correlation between PTH hormone and phosphorous (r = 0.37) in figure 3-16.

In addition to a negative correlation between PTH and blood calcium, (r = 0.3), as shown in figure 3-17, It is consistent with the results of previous studies

4.4.Effect of the Body Mass Index on Biomarker Parameters Levels in Acute Kidney Injury Patients

Acute kidney damage (AKI) is becoming more common in patients admitted to intensive care units (ICUs), The percentage of patients who develop AKI as a result of other complications ranges from 9% to more than 50% [185], Despite the advancement of renal replacement therapy (RRT), AKI continues to be a primary source of unfavorable outcomes [186], including high mortality [187], extended length of hospital and ICU stay, and worse quality of life [188].

Thyroid hormones are essential in metabolic pathways, and any imbalance in the amount of thyroid hormones causes direct metabolic disturbances in various organs, including the kidneys [189], because thyroid

hormones are critically required for the proper functioning and normal physiological growth of the kidneys. Any malfunction of the thyroid gland directly leads to adverse effects on kidney function [190].

The complete lack of thyroid hormone secretion causes a decrease in the basal metabolic rate by 40-30% from the normal rate and energy consumption, and thus leads to weight gain [191], Hypothyroidism is often associated with weight gain [192].

In this study, the majority of patients were within unacceptable ranges of body mass index, as normal weight was 35%, overweight 39%, and obese 26%.

Several epidemiological studies have suggested that the association between BMI and creatinine clearance is related to obesity and body fat intake [193,194,195].

Fernando Gerchman *et al*, 2009 [196], Koce *et al*, 2006 [197], The effects of obesity and body fat distribution on glomerular filtration rate were investigated, and it was shown that there is a positive association between creatinine clearance and BMI.

This result confirms the results of the current study in which BMI was directly related to creatinine clearance in AKI patients as shown in figure 3-18.

TSH levels are high or slightly increased in obese AKI patients and positively correlated with BMI with moderate increase in TSH and this is in line with the findings of this study where the highest concentration of TSH ,

T3and T4 is in the obese group [198,199], as shown in the figure 3-21, 3-22, 3-23

In the obese group, PTH levels in obese AKI patients were not statistically different, owing to the fact that patients with higher BMIs were more likely to be younger and have diabetes [200], have higher calcium levels and Phosphorous compared to the group of obesity and normal weight, It is consistent with the results of the study conducted by Kovesdy *et al* in (2007) [201], as shown in the figure3-19, 3-20, 3-24

A greater BMI was related with higher PTH levels [202], Studies have indicated that hyperparathyroidism was better connected with total body fat than with BMI, suggesting that obesity, not only increased body weight, was responsible for the identified relationships [203].

4.5.Effect of the Body Mass Index on Biomarker Levels in Chronic Kidney Disease Patients

Overweight or obesity is a notorious risk factor for mortality, disease and disability and has been linked to a number of diseases [204], especially kidney disease [205,206], in this study, patients were divided according to their body mass index into three groups: normal weight 50%, overweight 13%, and obesity group 37%, where many studies in both the United States [207], and European [208], have documented a close relationship between high BMI, risk of developing chronic kidney disease, low GFR, and consequently impaired ability of the kidneys to remove toxins and accumulate waste [209].

The current data indicated that the levels of urea and creatinine in the blood have a significant relationship with BMI, as we note that the highest

level of urea and creatinine is in the obese group as shown in figure 3-25 and 3-26, It is consistent with the results of the study conducted by Duan *et al* in (2015) [210], Dai *et al* in (2013) [212], Zarrati *et al* in (2019) [213].

The data of this study indicated that the highest level of T3, T4 hormone is in the overweight group and the lowest level in the obese group, in figure 3-29 and 3-30, It is consistent with the results of the study conducted by Urrea *et al* in (2022) [214], Adamska *et al* in (2022) [215], and this confirms that hypothyroidism has Link with BMI [216].

The current data indicated that the highest level of calcium is in the normal-weight and overweight group, in contrast to the obese group, as shown in figure 3-27.

This is consistent with the results of previous studies, where it was shown that people of normal weight have higher levels of calcium [217,218,219].

Several studies have investigated the relationship between obesity and hyperparathyroidism [220,221], which is presumed to be a consequence of calcium malabsorption as a result of vitamin D deficiency [222], that renal osteodystrophy and bone disease form due to increased uncontrolled bone turnover and thus decreased bone mineral density such as calcium and phosphorous and liberated in the blood [223,224].

The current data indicated that the highest level of phosphorous and PTH hormone is in the obese group, as shown in figures 3-28 and 3-31, It is consistent with the results of the study conducted by Altawil *et al* in (2021) [225].

4.6.Relation between Duration with Biomarker in AKI and CKD Patients

AKI is associated with progression to advanced CKD, in which we tested whether AKI patients' biomarkers could be affected by their hospital stay [185].

Figures 3-32 and 3-33 show a decrease in most of the vital signs of AKI patients with an increase in the length of their stay in the hospital while there was an increase in serum creatinine and PTH.

Patients suffer from increased hospitalization and may require dialysis, due to loss of kidney function and elevated levels of creatinine and metabolic acids because these levels have been associated with poor outcomes in a variety of diseases, including hypothyroidism [104].

Previous studies have shown that AKI patients who survive are at risk of developing CKD due to acute endothelial injury that leads to nephron damage followed by glomerular hypertrophy or progression of damage if acute renal failure persists [186].

The data of this study showed different levels of biomarkers for CKD patients as shown in figure 3-34 and 3-35.

The most characteristic of CKD patients with the passage of time is renal dystrophy resulting from hyperparathyroidism, which causes an increase in the rate of bone turnover [32], and this leads to the excretion of calcium and phosphorous from the bones and its deposition in the kidneys and blood vessels, and therefore it is one of the factors that cause cardiovascular diseases bloody [203

5.1. Conclusions

1-Hypothyroidism and parathyroid function disorders are common among individuals with renal insufficiency, particularly those with end-stage renal disease.

2-Hypothyroidism and parathyroidism were the most prevalent and positively associated with increased age and decreased GFR. In patients undergoing HD treatment.

3- It is important doing a regular examination of thyroid and parathyroid functions for patients with renal failure because early identification of thyroid disorders will help in better management of these patients

5.2. Recommendations

The study advises that it is to conduct future studies in the same field by looking for basing on the results offered in this work.

1. Follow-up of patients with renal failure who suffer from hypothyroidism and evaluate the function of the thyroid gland

2. A study of kidney function in hyperthyroidism and its comparison with those in hypothyroidism.

3.Follow-up of patients with renal failure who suffer from hyperparathyroidism and evaluate the function of the parathyroid glands

4. Study of kidney function in case of hyperparathyroidism and its comparison with the normal activity of the parathyroid glands

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الخلاصة

مقدمة موجزه: يصنف الفشل الكلوي إلى نوعين و هي إصابات الكلى الحادة وأمراض الكلى المزمنة. إصابة الكلى الحادة هي الانقطاع المفاجئ لوظائف الكلى في غضون أيام ، مصحوبة بارتفاع في اليوريا والكرياتينين في الدم ، وتراكم الفضلات النيتروجينية في مريض كانت وظائفه الكلوية طبيعية في السابق. في حين أن مرض الكلى المزمن هو تدهور في وظائف الكلى يحدث بشكل كلاسيكي يتطور على مدى أشهر أو سنوات. و يوصف بإنها تشوهات في وظائف الكلى تستمر لمدة ثلاثة أشهر أو أكثر لها العديد من الآثار الصحية ، والمعروفة أيضًا باسم مرض الكلى في المرحلة النهائية ، وهي حالة طبية تعمل فيها الكلى على الأقل بنسبة 15٪ من المستويات الطبيعية.

هدف الدراسة: تقييم هرمون الغدة الدرقية و تشمل Triiodothyronine و Thyroxine و Thyroid stimulating hormone بالإضافة إلى هرمون Parathyroid hormone في مرضى إصابات الكلى الحادة ومرضى الكلى المزمنة ومقارنتها مع مجموعة التحكم وتقييم الكالسيوم والفوسفور في مرضى الكلى الحادة. الإصابة والمرضى الذين يعانون من أمراض الكلى المزمنة ومقارنتها مع المجموعة الضابطة وإيجاد علاقة ارتباط بين هرمون الغدة الدرقية وهرمون الغدة الجار درقية لمرضى إصابات الكلى الحادة ومرضى أمراض الكلى المزمنة.

العينات والطرائق العمل: أجريت هذه الدراسة في مستشفى الإمام الصادق التعليمي بمحافظة بابل في الفترة ما بين (تشرين الأول 2021) إلى (نيسان 2022) على ستين مريضاً يعانون من الفشل الكلوي ، 30 منهم يعانون من إصابات الكلى الحادة و 30اخرون يعانون من مرض الكلى المزمن بالإضافة إلى 40 شخصًا عاديًا كمجموعة ضابطة ، تراوحت أعمارهم بين 20-69 عامًا من حيث الجنس ، معظمهم من الذكور ، 33 ذكرًا و 27 أنثى. تم قياس هرمون Thyroid stimulating hormone و Triiodothyronine و Thyroxine باستخدام طريقة ELISA باستخدام جهاز Mini Vidas و قياس هرمون Parathyroid hormone باستخدام جهاز Cobas

النتائج: أظهرت نتائج الدراسة أن هناك علاقة بين هرمونات الغدة الدرقية وهرمونات الغدة الجار درقية مع مرض الفشل الكلوي ، ووجد فرق كبير في Thyroid stimulating hormone و Triiodothyronine و Thyroxine مقارنة بالمجموعة الضابطة ، أدى قصور الغدة الدرقية إلى

زيـــادة هرمـــون Thyroid stimulating hormone و انخفـــاض فـــي مســـتويات Triiodothyronine و Thyroxine مقارنـة بالمجموعـة الضـابطة ، ويصـاحب ذلك انخفاض في معدل الترشيح الكبيبي ، وأدى فرط نشاط جارات الدرقيـة إلـى زيـادة إفراز هرمون Parathyroid hormone المصحوب بفرط فوسفات الدم. الدم ونقص كالسيوم الدم ، تمت مقارنـة هذه النتـائج مـع المجموعة الضابطة ، والتي أظهرت فرقاً معنوياً (P = 0.01) لمعظم اختبارات هذه الدراسـة ، بينمـا كان هناك فرق بسيط (P = 0.01) لهرمون Triiodothyronin عند مقارنتها مع مجموعة التحكم لكل من مجموعات AKI و CKD. نتائج الدراسة آثار واضحة لكبار السن الذين يعـانون مـن الفشل الكلوي ، حيث تم تقسيم مرضـى القصـور الكلوي الحاد ومرضـى الكلى المزمن إلـى فئتين عمـريتين ، الأولى من 20-40 سنة ، والثانيـة من 41 إلـى 69 سـنة وعند مقارنـة هذه المجـاميع مـع المجموعـة الضابطة أظهرت فرق معنوي p = 0.001 ، حيث أظهرت النتائج أن مؤشر كتلة الجسم كان له دور في التأثير على المؤشرات البيوكيميائية ، حيث تم تقسيمهم إلى ثلاث مجموعات حسب الوزن: الوزن الطبيعي ، الوزن الزائد ، السمنة المرضية. كلوي.

الاسـتنتاجات: قصـور الغـدة الدرقيـة واضـطرابات وظـائف الغـدة الجـار درقيـة شـائعة بـين الأفـراد المصابين بقصـور كلـوي ، وخاصـة أولئك الـذين يعـانون مـن مـرض الكلـى فـي نهايـة المرحلـة. كـان قصور الغدة الدرقية والغدة جار الدرقية الأكثر انتشارًا ومرتبطًا إيجابيًا بزيادة العمر وانخفاض معدل الترشيح الكبيبي. في المرضـى الذين يخضـعون لعـلاج غسيل الكلـى. مـن المهم إجـراء فحـص دوري لوظائف الغدة الدرقية والغدة الدرقيـة للمرضـى الـذين يعـانون مـن الفشل الكلـوي لأن التحديد المبكر لاضطرابات الغدة الدرقية سيساعد في إدارة أفضل لهؤلاء المرضى.

جامعة كربلاء

دراسة هرمونات الغدة الدرقية والجارات الدرقية بين مرضى القصور الكلوي الحاد ومرض الكلى المزمن

رسالة مقدمة الى

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

من قبل الطالب

سجاد احمد كاظم

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