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CORRELATION BETWEEN PARATHYROID GLAND WITH SOME BIOCHEMICAL PARAMETERS IN THALASSEMIA PATIENTS

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DOAA FALIH IBRAHIM AL-HUMAIRI

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CORRELATION BETWEEN PARATHYROID GLANDS WITH SOME BIOCHEMICAL PARAMETERS IN THALASSEMIA PATIENTS

By Doaa Falih Ibrahim AL-HUMAIRI

April 2022

As proof of our reading and evaluation of this thesis, we certify that it is competent, both in scope and in quality, for the degree of Master of Science

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Doaa Falih Ibrahim AL-HUMAIRI

ABSTRACT

CORRELATION BETWEEN PARATHYROID GLANDS WITH SOME BIOCHEMICAL PARAMETERS IN THALASSEMIA PATIENTS

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Master of Science in Chemistry

Advisor: Prof. Dr. Volkan EYÜPOĞLU

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The main goal of this research is to assess the correlation between parathyroid glands with some biochemical parameters in thalassemia patients, and study the potential increase in thalassemia risk factors when PTH increased or decreased, measurement of some biochemical tests concentration in Women. 130 patients (65 Women with thalassemia and 65 without thalassemia) with varying degrees of disease activity matched for age, sex, and body mass index will be evaluated. Thalassemia is considered one of the diseases that spread in the south and the center of Iraq. The present results with respect to age and random blood sugar percentage indicate that there is no statistical significance in diagnosing the disease, but age remains related to the development of the disease. Also, there was no correlation between age and parathyroid hormone when Pearson's test was performed. Also, there was no statistical significance for triglycerides and low-density fats. On the contrary, there is great importance for the test of parathyroid hormone and lipids, and it may have a great role in diagnosing the disease or a little deterioration of the patient's condition. There was a correlation between WBC, Hb, total cholesterol, PTH/ Hb, and parathyroid hormone when Pearson's test was performed.

2022, 32 pages

Keywords: Parathyroid glands, Thalassemia, PTH, Biochemical parameters

ÖZET

TALASEMİ HASTALARINDA PARATİROİD BEZLERİ İLE BAZI BİYOKİMYASAL PARAMETRELER ARASINDAKİ KORELASYON

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Ocak 2022

Bu çalışmanın temel amacı, talasemi hastalarında paratiroid bezlerinin bazı biyokimyasal parametrelerle ilişkisini değerlendirmek ve kadınlarda bazı biyokimyasal test konsantrasyonlarının PTH'nin artması veya azalması durumunda talasemi risk faktörlerindeki potansiyel artışı incelemektir. Yaş, cinsiyet ve vücut kitle indeksi açısından farklı derecelerde hastalık aktivitesi olan 130 hasta (65 Talasemili ve 65 Talasemili Kadın) değerlendirilendirilmiştir. Talasemi, Irak'ın güneyinde ve merkezinde yayılan hastalıklardan biri olarak kabul edilmektedir. Yaş ve rastgele kan şekeri yüzdesi ile ilgili mevcut sonuçlar, hastalığın teşhisinde istatistiksel bir anlamlılık olmadığını, ancak yaşın hastalığın gelişimi ile ilişkili olduğunu göstermektedir. Ayrıca Pearson testi yapıldığında yaş ile paratiroid hormonu arasında ilişki tespit edilememiştir. Ayrıca trigliseritler ve düşük yoğunluklu yağlar için istatistiksel bir anlam bulunamamıştır. Aksine paratiroid hormon ve lipid testinin önemi büyüktür ve hastalığın teşhis edilmesinde ya da hastanın durumunun biraz kötüleşmesinde büyük rolü olabileceğine dair sonuçlar elde edilmiştir. Pearson testi yapıldığında WBC, Hb, total kolesterol, PTH/Hb ve paratiroid hormonu arasında bir korelasyonun varlığı tespit edilmiştir.

2022, 32 sayfa

Anahtar Kelimeler: Paratiroid bezleri, Talasemi, PTH, Biyokimyasal parametreler

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Doaa Falih Ibrahim AL-HUMAIRI

Çankırı-2022

CONTENTS

LIST OF SYMBOLS

%	Percent
±	Plus minus
°C	Degrees Celcium
µg	Migrogram
µL	Microliter
g	Gram
h	Hour
kg	Kilogram
mg	Miligram
mL	Mililitter

LIST OF ABBREVIATIONS

GFR	Glomerular filtration rate
HDL	High-density lipoprotein
HPT	Hypoparathyroidism
HRP	Horseradish Peroxidase
IV	Intravenous
LDL	Low-density lipoprotein
PTH	Parathyroid hormone
VLDL	Very low-density lipoprotein

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1. INTRODUCTION

Thalassemia is a broad group of genetic abnormalities of hemoglobin production that affects people of all ages. It is characterized by the lack or decreased synthesis of one or more kinds of globin chains, which may be either total or partial. Hepatosplenomegaly manifests itself in the form of pallor, stunted development, and belly enlargement in the afflicted newborns. When left untreated, distinctive bone alterations emerge in children, including thinning of the cortex of long bones, expansion of medullary gaps, and separation of the orbit (Risoluti *et al.* 2018). When it comes to severe thalassemia, the mainstay of therapy is frequent blood transfusion, with an emphasis on maintaining hemoglobin levels more than 10 g/dL. Citrate poisoning occurs as a consequence of repeated blood transfusion, which may lead to iron accumulation in the parathyroid gland, which can result in hypoparathyroidism. According to a few studies, some thalassemic patients receiving frequent PCV infusions lead to hypoparathyroidism, particularly beyond the age of ten years. Low vitamin D and parathyroid hormone (PTH) levels have been seen in people suffering from hypoparathyroidism. Vitamin D and calcium Supplementation, according to a small number of research, has also been proven to enhance blood calcium status. A lack of data and studies in the Indian population prompted us to design this study, in which serum PTH, serum and urinary calcium levels were measured in children with thalassemia major who were receiving packed cells transfusion therapy. It has been found that vitamin D and calcium supplementation had no effect on serum PTH or serum and urinary calcium levels (Fancy *et al.* 2010).

1.1 Aim of Study

The study aims at assessing the Correlation between parathyroid glands with some biochemical parameters in thalassemia patients, and study the potential increase in thalassemia risk factors when PTH increased or decreased, measurement of some biochemical tests concentration in Women.

2. LITERATURE REVIEW

2.1 Parathyroid Glands

2.1.1 Overview

They are little, pea-sized glands that are located in the neck, just underneath the butterfly-shaped thyroid gland. They create hormones that aid the body in temperature regulation. The majority of individuals have four parathyroid glands, two behind each 'wing' of the thyroid gland. The parathyroid glands are responsible for the production of a hormone known as parathyroid hormone. The endocrine system contains four small glands called parathyroid glands, which regulate the amount of calcium in our bodies (Peissig *et al.* 2018). When they are normal size, parathyroid glands (of which we all have four) are about the size of a grain of rice. They can grow to be as large as a pea on occasion and still be considered normal. Each of the four parathyroid glands, which are located behind the thyroid, is represented by the mustard yellow glands that are visible behind the pink thyroid gland in this illustration. The trachea is represented by the light blue tube that runs up the center of the picture (wind pipe). The voice box is represented by the pink structure at the top of the image, which sits on top of the trachea (windpipe). It is depicted on both sides of the thyroid as the carotid arteries, which run from the heart up to and through the brain (Lorente-Poch *et al.* 2015).

The parathyroid glands can be found on the backside of the thyroid gland. Keep in mind that Behind the thyroid are the parathyroid glands. This illustration shows three little (normal) parathyroid glands and one giant sick parathyroid gland in which one develops into a tumor and produces an excessive amount of hormone (parathyroidism). It is very likely that have parathyroid disease if have three normal parathyroid glands. An operation will be required if have parathyroid disease (hyperparathyroidism), in which case the one parathyroid gland that has developed into a tumor will be removed. Despite the fact that they are neighbors and that Despite the fact that they are both components of the endocrine system, the thyroid and parathyroid glands are unrelated and serve different functions; they simply have names that are similar and confusing (Ladurner *et al.* 2017).

2.1.2 Function

The generation of parathyroid hormone, which regulates calcium levels in the circulation, is the responsibility of the parathyroid glands. Small changes in calcium levels in the human body may induce muscle and nerve diseases, therefore maintaining accurate calcium levels is critical. The parathyroid hormone promotes the following functions: the release of calcium from the bones into the circulation, the production of parathyroid hormone, and the production of parathyroid hormone. The intestines are in charge of calcium absorption from food. Calcium conservation is the responsibility of the kidneys. This vitamin D supplement increases the formation of cells in the kidney that convert less efficient forms of vitamin D into the most effective version for absorbing calcium from the intestines (Thomas *et al.* 2018).

They, however, regulate the calcium levels in blood, bones, and other tissues. The level is controlled by the production of a hormone called Parathyroid Hormone by PTH. The fact that calcium is the most significant element means that calcium is controlled more strictly than any other element in our bodies. The only element that has its own regulatory mechanism is calcium, which is controlled by the parathyroid glands (Michaud *et al.* 2014). Parathyroid hormone has the greatest influence on the bones and kidneys, which are the primary organs on which it acts. When calcium levels in the blood are low, parathyroid hormone is released into the circulation by the parathyroid glands, which stimulates the bones to release calcium and cause calcium levels in the bloodstream to rise. The kidneys are also stimulated, which helps to prevent calcium from being excreted in the urine. It also helps to improve vitamin D metabolism by activating the kidneys (Chang and Lang 2017).

2.1.3 Anatomy

These glands are positioned on the posterior portion of the thyroid gland, and they are responsible for producing thyroid hormone. This group of cells is flattened and oval in form, and they are located outside of the thyroid gland itself, but inside the pretracheal fascia. Usually, there are glands, while there is considerable diversity in number (ranging

from two to six). It is believed that the superior parathyroid glands are descended from the fourth pharyngeal pouch. Their position is around one centimeter above and to the right of where the inferior thyroid artery makes its entry into the thyroid gland, near the center of each thyroid lobe's posterior border (Alesina *et al.* 2018). The inferior parathyroid glands are produced from the third pharyngeal pouch, which is located in the neck of the neck. However, the inferior parathyroid glands are frequently situated towards the inferior poles of the thyroid gland, despite the fact that their placement varies from person to individual. It is possible to find the inferior parathyroid glands as far inferiorly as the superior mediastinum in a tiny percentage of the population (Demarchi *et al.* 2020).

The parathyroid glands might produce an excessive amount of parathyroid hormone at times. Patients may have an abnormally high calcium level in their blood (hypercalcemia), which may cause them to feel generally poorly; however, they may not experience any symptoms in this situation. Increased thirst, increased urine output, stomach discomfort, constipation, generalized aches and pains, and changes in mood are some of the symptoms that may occur. One of the most prevalent conditions that causes this is referred to as primary hyperparathyroidism. It may take many months to get a diagnosis since other possible reasons of elevated calcium levels in the blood must be ruled out. Removal of the hyperactive parathyroid gland or conservative management of the condition are options for treatment (Treglia *et al.* 2019).

In certain cases, if a high level of parathyroid hormone is not recognized for a lengthy period of time, it may cause calcium to be lost from the bones into the bloodstream and then into the urine. This may ultimately result in bones becoming brittle (osteoporosis). Calcium stones in the kidney may also be caused by an excessive amount of calcium in the urine. On rare occasions, the parathyroid glands may not release enough parathyroid hormone, resulting in low calcium levels in the bloodstream (hypocalcaemia). Hypoparathyroidism is the medical term for this ailment. After neck surgery, such as for thyroid problems, this is the most frequent complication. Tingling, 'pins and needles' sensations, and muscular cramps/spasms are all symptoms of low calcium levels in the blood. Vitamin D or calcium supplements may be prescribed as part of the treatment (Benmiloud *et al.* 2020).

2.1.4 Role of calcium in human body

The parathyroid glands' only purpose is to control calcium levels in our bodies within a narrow range, enabling our neurological and muscular systems to function correctly. They have no other function. The parathyroid glands monitor the amount of calcium in the blood every minute of every day, and if the calcium levels begin to fall, the parathyroid glands produce PTH, which travels to the bones and draws calcium out (making a withdrawal from the calcium vault) and releases it into the bloodstream. The parathyroids shut down and stop manufacturing parathyroid hormone when the calcium level in the blood reaches a certain level (PTH) (Kahramangil and Berber 2017).

An over-active one or more of the parathyroid glands that produce excessive parathyroid hormone results in a potentially dangerous calcium imbalance, which is the single most common parathyroid condition in the world. For the purpose of supplying electrical energy to our neurological system. The most significant thing that calcium accomplishes in the human body is to create a pathway for electrical impulses to pass through nerves, which is very crucial. Calcium is the electrical conductor that our nervous system utilizes to communicate with the rest of our body. As a result, the nervous system is the site of the majority of the symptoms associated with parathyroid illness and elevated calcium levels (depression, weakness, tiredness, etc). There is a lot more information on the symptoms of parathyroid illness on another website (Grimaldi *et al.* 2018).

2.2 Parathyroid Hormone (PTH)

It is produced by four parathyroid glands positioned beneath the thyroid gland. In most cases, parathyroid hormone controls calcium levels in the blood, mostly by boosting calcium levels when they become dangerously low. It does this by the activities of its constituents on the kidneys, bones, and intestinal tract. The parathyroid hormone is a hormone that increases the release of calcium from massive calcium deposits in the bones into the circulation, which is essential for bone health. Bone degradation rises as a result, and the production of new bone is decreased. The parathyroid hormone is responsible for reducing calcium excretion in the urine. The generation of active vitamin D in the kidneys

is stimulated by parathyroid hormone, on the other hand. Aside from that, the hormone indirectly enhances calcium absorption from meals in the stomach as a result of its effects on vitamin D metabolism, which is a beneficial outcome (Gschwandtner *et al.* 2018).

The production of parathyroid hormone is primarily regulated by the undesirable feedback loop between calcium levels and the parathyroid glands themselves. Low levels in the blood increase the production of parathyroid hormone, while high calcium levels in the blood inhibit the release of parathyroid hormone (parathyroidism). This condition is also referred to as primary hyperparathyroidism. There is a disorder termed tertiary hyperparathyroidism, which is similar to primary hyperparathyroidism but considerably more uncommon. It produces hypercalcemia as a result of excessive parathyroid hormone production on the backdrop of all four glands being hyperactive. Secondary hyperparathyroidism is a condition that arises in reaction to low calcium levels in the blood and may be caused by a variety of factors, including renal illness and vitamin D insufficiency (Wein and Kronenberg 2018).

2.3 Biochemical Parameters

2.3.1 Serum total and ionized calcium

Calcium is a vital mineral that the body utilizes in a variety of functions. It improves the strength of the bones and teeth, as well as the operation of the muscles and nerves, among other things. A serum calcium blood test determines the amount of calcium present in the bloodstream. The blood contains many calcium salts, each of which has a distinct structure. Calcium ions, calcium bound to other minerals (known as anions), and calcium attached to proteins (such as albumin) are all examples of calcium forms. Ionized calcium, commonly referred to as free calcium, is the most active form of mineral calcium. A serum calcium test is often used to determine the total quantity of calcium present in the blood. Calcium ions, calcium linked to proteins and anions, and calcium ions in solution are all included. Depending on whether have evidence of renal illness, some types of cancer, or difficulties with the parathyroid gland, the doctor may want to monitor the calcium levels in the blood (Thongprayoon *et al.* 2020).

Increased amounts of ionized calcium provide additional information about active ionized calcium. If have aberrant quantities of proteins in the blood, such as albumin or immunoglobins, it may be necessary to know the ionized calcium concentrations. If the balance between bound calcium and free calcium is out of the ordinary, it is critical to determine the cause. In most cases, free calcium and bound calcium each account for half of the total calcium in the body. An imbalance might be a symptom of a more serious health problem (Cappellini *et al.* 2020). If getting blood transfusions, are severely sick and receiving intravenous (IV) fluids, the undergoing major surgery, or have abnormal levels of blood proteins, may need to have the ionized calcium level evaluated. In these situations, it's critical to understand just how much free calcium have accessible in the system (Jassam *et al.* 2020).

When the free calcium levels are low, the heart rate might slow down or speed up, can have muscular spasms, and can even go into a coma. If experience any indications of numbness around the lips or in the hands and feet, or if have muscular spasms in the same locations, the doctor may request an ionized calcium test to rule out any underlying conditions. These are signs that the free calcium levels are low (Turner *et al.* 2020). It is more difficult to execute an ionized calcium test than it is to do a serum calcium test. Blood samples must be handled in a certain manner, and this is only done under particular circumstances (Moore *et al.* 2020). A tiny sample of the blood is required for an ionized calcium test. A venipuncture will be performed by a healthcare expert in order to get a blood sample. It is necessary for them to clean an area of skin on the arm or hand before inserting a needle into a vein through the skin and drawing a little volume of blood into a test tube (Blomberg *et al.* 2016).

2.3.2 Parathyroid hormone concentration

Ca and phosphorus concentrations in extracellular fluid are regulated by parathyroid hormone, which is the most significant endocrine regulator of both concentrations. This hormone is released by cells of the parathyroid glands and has the majority of its target cells in the bones and kidney, among other places. Parathyroid hormone-related protein is another hormone that interacts with the same receptor as parathyroid hormone and has

significant developmental consequences (Thongprayoon *et al.* 2020). Parathyroid hormone is generated as a preprohormone, much as the majority of other protein hormones. Following intracellular processing, the mature hormone is packed inside the Golgi apparatus into secretory vesicles, which are then discharged into the bloodstream via the process of exocytosis. Parathyroid hormone is released as a linear protein of 84 amino acids, which is known as parathyroid hormone (Zhao *et al.* 2019).

The hormone has an easy-to-understand job description, which states that it must restore calcium ion concentrations in extracellular fluid to normal levels if they fall below normal. Increases in calcium concentration are associated with a decrease in the concentration of the phosphate ion in the bloodstream. The parathyroid hormone performs its function by triggering at least three different processes. It is undeniable that increasing calcium absorption from the small intestine would result in higher calcium levels in the blood. This process is stimulated by parathyroid hormone, which does so indirectly by boosting the creation of the active form of vitamin D in the kidney. Vitamin D stimulates the production of a calcium-binding protein in intestinal epithelial cells, which helps to ensure that calcium is absorbed efficiently into the bloodstream (Wein *et al.* 2018).

In addition to promoting calcium fluxes into the bloodstream from the bones and intestines, parathyroid hormone acts as a brake on calcium excretion in urine, allowing calcium levels in the blood to remain stable. The stimulation of tubular reabsorption of calcium is responsible for this action. Another action of parathyroid hormone on the kidney is that it stimulates the excretion of phosphate ions in the urine, which is beneficial. In reaction to low extracellular calcium concentrations, parathyroid hormone is released into the blood stream. Even though variations in blood phosphate content may be connected with changes in parathyroid hormone release, this seems to be a secondary consequence, and phosphate does not appear to be a substantial regulator of this hormone in its natural state. In response to calcium concentrations falling below the normal range, the release of parathyroid hormone increases by a significant amount. Even when calcium levels in the blood are high, only low quantities of the hormone are released. The image on the right displays the release of parathyroid hormone from cells cultivated in vitro in

various calcium concentrations, as measured by the some method (Souberbielle *et al.* 2017).

The extracellular free calcium content of the parathyroid cell is monitored by an integral membrane protein that serves as a calcium-sensing receptor in the parathyroid cell. In both cases, excessive release of parathyroid hormone might be seen. It is caused by parathyroid gland pathology, most frequently a tumor (adenoma) that secretes the hormone without normal control. Secondary hyperparathyroidism is caused by a malfunctioning parathyroid gland. Chronic rises in calcium levels in the blood (hypercalcemia), kidney stones, and decalcification of bone are all common signs of this condition. In cases of secondary hyperparathyroidism, a condition outside of the parathyroid gland results in an excessive release of parathyroid hormone, which is harmful to the body. A typical cause of this problem is renal disease - if the kidneys are unable to reabsorb calcium from the bloodstream, blood calcium levels will decline, causing the body to secrete parathyroid hormone on a continuous basis in order to maintain normal calcium levels in the bloodstream. Secondary hyperparathyroidism may also occur as a consequence of poor nutrition, such as diets that are lacking in calcium or vitamin D, or diets that include an excessive amount of phosphorus, for example (e.g. all meat diets for carnivores). Decalcification of bone is a significant consequence of secondary hyperparathyroidism, which may result in pathologic fractures or "rubber bones" (Pal *et al.* 2019).

No doubt, chronic production or continuous infusion of parathyroid hormone causes bone decalcification and bone mass loss, as well as bone marrow failure. Treatment with parathyroid hormone, on the other hand, can actually result in an increase in bone mass and bone strength in some cases when used properly. It seems that when the hormone is supplied in pulses (for example, via once daily injection), this apparently counterintuitive effect happens, and that this kind of treatment looks to be an effective therapy for illnesses such as osteoporosis. Hypoparathyroidism is characterized by insufficient synthesis of parathyroid hormone, which leads in lower calcium concentrations and increased phosphorus concentrations in the blood. The removal of the parathyroid glands surgically and disease processes that lead to the loss of the parathyroid glands are two of the most

common causes of this condition. The hypocalcemia that results is often accompanied with tetany and convulsions, and it may be immediately life-threatening. Calcium infusions, oral calcium supplements, and vitamin D treatment are all used to help patients regain normal calcium levels in their blood (Wang *et al.* 2019).

2.3.3 Phosphate

A phosphate test is used to determine the quantity of phosphate present in a sample of blood. Phosphate is a charged particle (ion) that includes the mineral phosphorus and is responsible for its charge. Phosphorus is required by the body for the development and repair of bones and teeth, as well as for the proper functioning of neurons and the contraction of muscles. The majority of the phosphorus included in phosphate (about 85 percent) is found in bones. The remainder of it is kept in tissues throughout the body as described above. The kidneys are involved in the regulation of the quantity of phosphate in the blood. Extra phosphate is filtered out of the body by the kidneys and excreted via the urine stream. When there is an excessive amount of phosphate in the blood, it is typically due to a renal disease (Lyngsie *et al.* 2019). The quantity of phosphate present in the blood has an effect on the amount of calcium present in the blood. Calcium and phosphate in the body respond in a diametrically opposed manner: when blood calcium levels increase, blood phosphate levels decrease and vice versa. A hormone known as parathyroid hormone (PTH) is responsible for regulating the amounts of calcium and phosphorus in the bloodstream. An evaluation of vitamin D levels, as well as PTH levels, are performed at the same time as an evaluation of phosphorus levels, as well. In order for the body to absorb phosphate, must have enough vitamin D (Ley *et al.* 2019).

When analyzing the calcemic response to PTH, phosphorus is an essential aspect to consider. Albright shown many years ago that the initial activity of infused parathyroid extract was phosphaturia, which was followed by a decrease in serum phosphorus before a calcemic effect emerged as a result. Increased phosphate concentrations in the medium were shown to inhibit calcium outflow from bone in an ex-vivo research, which was conducted both in the absence and presence of PTH. In addition, phosphate has been shown to alter calcium efflux from bone in both animal and human investigations

(Gandolfi *et al.* 2015). Change from a normal phosphate diet and a fixed replacement dosage of PTH adequate to maintain normal blood calcium and phosphorus levels in parathyroidectomized rats to a high-phosphate diet caused hypocalcemia and hyperphosphatemia, respectively. The development of hypocalcemia and hyperphosphatemia in ng, healthy subjects following a continuous intravenous phosphate infusion for seven days was followed by a three-fold increase in PTH, which increased phosphate excretion by five-fold and restored normal serum calcium and phosphorus levels. In contrast, phosphate deprivation results in hypercalcemia despite a significant reduction in PTH levels. Even high dosage bisphosphonate administered to phosphate-depleted animals failed to prevent hypercalcemia, despite the fact that it had toxic effects on osteoclasts and a significant decrease in the surface of the osteoblasts (Baird *et al.* 2015).

These findings provide credence to the hypothesis that an osteoclast-independent action may be critical for calcium efflux from the bone. To conclude, bisphosphonate therapy of phosphorus deficient rats increased urine calcium excretion more than treatment of phosphate deficient rats that did not receive bisphosphonates, indicating that reduced calcium influx to bone may be a contributing cause. Some disorders and infections may cause the relationship between calcium and phosphate to become distorted. In order to account for this, the levels of phosphate and calcium are often tested at the same time. It is possible that may need this test to assess the phosphate levels if have renal illness or bone disease. It aids in the identification of issues with specific glands, such as the parathyroid glands. The test is also used to determine the root cause of aberrant vitamin D levels in the blood (Miles *et al.* 2015).

2.3.4 Magnesium

Magnesium boosts the production of a specific hormone, calcitonin, which helps to maintain bone structure by drawing calcium from the blood and soft tissues and redistributing it to the bones, so avoiding osteoporosis, certain kinds of arthritis, and kidney stones. It is required for the metabolism of vitamin D and has an impact on the body's consumption of vitamin D by increasing the activity of cellular enzymes in the

body. Enzymes are protein molecules that function as catalysts in the body, stimulating every chemical process that occurs. Magnesium is required by all of the enzymes that metabolize vitamin D. Magnesium may have a role in the immune system's response to vitamin D, according to several research (Al Alawi *et al.* 2018). The production of active vitamin, on the other hand, is increased by the hormone parathyroid hormone. Due to the fact that magnesium insufficiency is a significant component in the outcomes achieved from vitamin D supplementation, the efficacy and advantages of vitamin D are significantly reduced in the absence of appropriate magnesium levels in the body. Magnesium interacts with and is required for the functioning of vitamin D, despite the fact that the majority of individuals do not consume the necessary daily dose of this crucial mineral (Feeney *et al.* 2016). Since the beginning of pathology's examination of the heart, it has been clear that there is a link between calcium deposits and the development of cardiac disease. Vitamin D prevents calcium deposition in the arteries, while magnesium transforms vitamin D into its active form, allowing it to prevent calcium accumulation in cholesterol plaque in the arteries. Vitamin D and magnesium work together to prevent calcium deposition in the arteries. Calcium is required for the development of a healthy bone structure in Figure 2.1 (Mousa *et al.* 2015, Heydary *et al.* 2015).

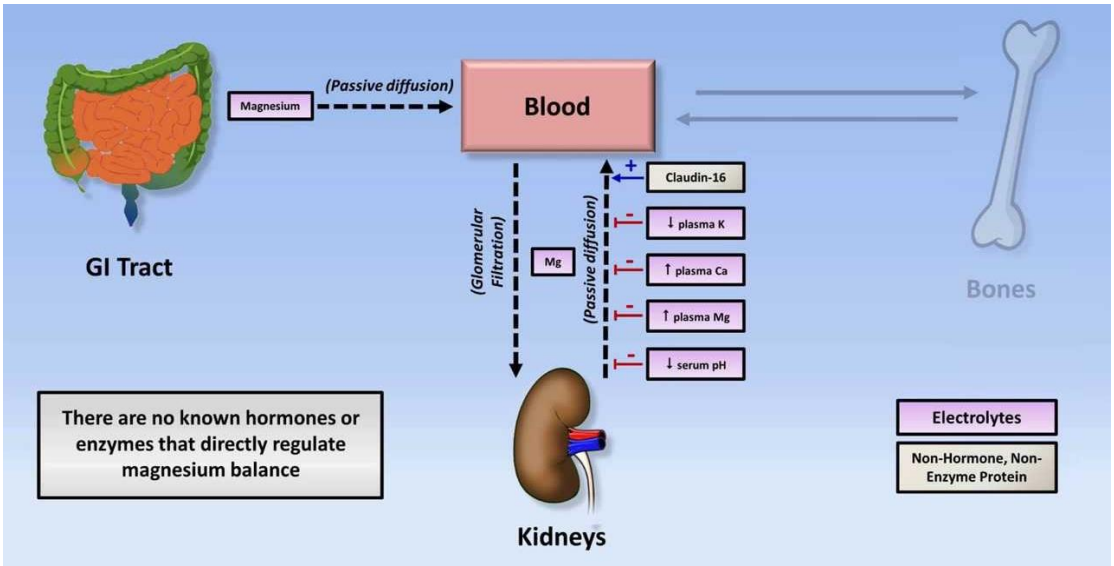

Figure 2.1 Regulation of magnesium (Lu *et al.* 2017)

2.3.5 Creatinine

When get a creatinine test based on the creatinine structure in Figure 2.2, the kidneys are evaluated to see how effectively they are doing their job of filtering waste from the blood. It is a chemical substance produced by the energy-producing activities in the muscles that is excreted in urine. The kidneys are responsible for filtering creatinine from the blood. Creatinine is excreted from the body as a waste product via the urine. To keep track of the therapy or course of renal disease, to keep an eye out for pharmacological side effects that might include kidney damage or impaired renal function, as well as to prevent kidney damage from occurring. In order to keep track of the function of a donated kidney. Creatinine enters the circulation and is filtered out of the bloodstream at a rather consistent pace, unless anything unusual happens. Should be able to maintain a somewhat constant level of creatinine in the blood. A high amount of creatinine may indicate that the kidneys aren't working properly (Tseng *et al.* 2018). Additionally, the measurement of serum creatinine may be used to determine how rapidly the kidneys filter blood (glomerular filtration rate). A higher GFR may offer a more accurate readout on renal function than serum creatinine because of the fluctuation in serum creatinine from one individual to another. The serum creatinine count, as well as other parameters such as age and gender, are taken into consideration in the GFR calculation algorithm. A GFR score of less than 60 indicates renal disease. The range of scores below 60 may be used to track the progress of therapy and the course of illness (Ellairaja *et al.* 2017).

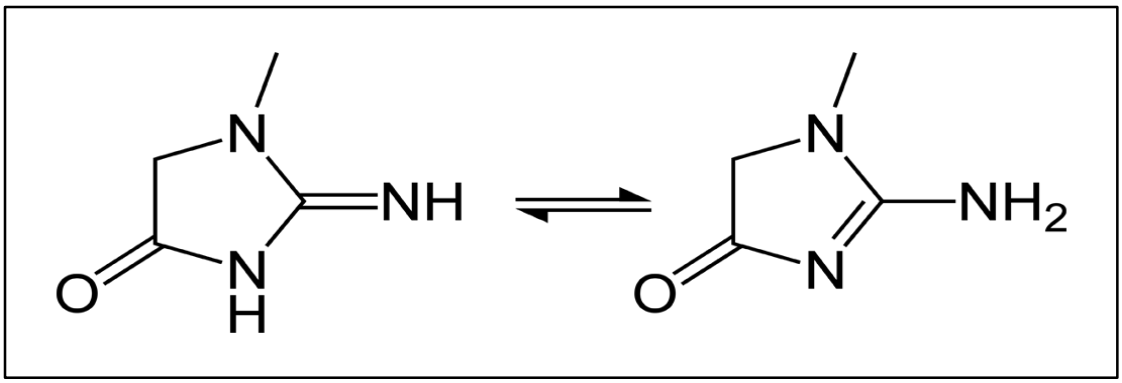

Figure 2.2 The chemical structure of creatine (Cánovas *et al.* 2019)

3. MATERIALS AND METHODS

3.1 Materials

3.1.1 Instrument and materials

The intruments, material, Kits, and chemical that used in the present study are described in the Table 3.1 and Table 3.2.

Table 3.1 The instrument, materials, and its company

No	Instrument and Material	Company
1	Cobas C111	Rouch
2	Cobas E411	Rouch
3	Spectrophotometer	China
4	Automatic Pipette	China
5	White tube	China
6	Gel Tube	China
7	Yellow - Blue Tip	China
8	Incubator	China
9	CBC- Swlab	uede

Table 3.2 Kits and chemical material

No	Kits	Use
1	PTH (Pg/mL)	Measurement of PTH
2	Ca (mg/dL)	Measurement of calcium
3	WBC	Measurement by CBC
4	Hb(g/dL)	Measurement by CBC
5	Platelete	Measurement by CBC
6	RBS (mg/dL)	Measurement of glocuse
7	Total cholestrol (mg/dL)	Measurement of Tc
8	Triglyceride (mg/dL)	Measurement of Tg
9	HDL (mg/dL)	Measurement of HDL

3.1.2 Studied groups

The present study included the selection of 130 patiens (65 Women with thalassemia and 65 without thalassemia) with varying degrees of disease activity matched for age, sex and body mass index will be evaluated.

Group A : 65 Women with thalassemia (Patients Groups).
Group C : 65 Women without thalassemia (Controls group).

3.2 Methods

3.2.1 Human parathyroid hormone ELISA Kit - MBS702413

The PTH concentrations in blood, plasma, and tissue homogenates may be determined quantitatively using this kit.

The assay's basic principle

Specifically, the quantitative sandwich enzyme immunoassay approach is used in this test. A microplate has been pre-coated with an antibody that is specific for PTH. Pipettes are used to transfer standard and sample solutions into the wells, and any PTH present is bound by the immobilized antibody. After any unbound compounds have been removed from the wells, a biotin-conjugated antibody specific for PTH is added to the wells. After washing, the wells are incubated with avidin conjugated Horseradish Peroxidase (HRP), which reacts with avidin. An avidin-enzyme reagent is added to the wells after a wash to remove any unbound avidin-enzyme reagent, and color develops in proportion to the quantity of PTH bound during the first stage. It is necessary to interrupt the color development process in order to measure the intensity of the color.

3.2.2 Materials provided

The total number of reagents Plate for assaying (12 x 8 coated Microwells), As is customary in the field (Freeze dried) Antibodies to biotin (100 x concentrate) 1 × HRP-avidin (120 mL) (100 x concentrate) biotin-antibody Diluent (1 x 120 mL) Diluent for HRP-avidin (about 15 mL). Sample Diluent (one 15 mL volume). Wash Buffer (50 mL): 1 x (25 x concentrate) 1. one TMB (20 mL) of the desired concentration Substrate stop

solution (ten milliliters) a single adhesive strip measuring 10 mL (For 96 wells); manual Instruction 1.

Assay procedure

Before using any reagents or samples, allow them to come to room temperature. Centrifuge the material once more once it has been thawed before use in the experiment. It is suggested that all samples and standards be analyzed in triplicate to ensure the highest level of accuracy.

Prepare all of the reagents, working standards, and samples in the manner described in the preceding parts of this chapter.

1. Use the Assay Layout Sheet to calculate the number of wells to be used, then place any residual wells and desiccant back into the pouch and ziploc bag, and store the unused wells at 4°C until they are needed.
2. Fill each well with 100 mL of standard and sample. Use the adhesive strip that was supplied to secure the cover. Incubate for 2 hours at 37 degrees Celsius. A plate arrangement is supplied for keeping track of the standards and samples that have been tested.
3. Remove the liquid from each well without washing it.
4. Fill each well with 100 mL of Biotin-antibody (1x). Replace the old sticky strip with a fresh one. Incubate for 1 hour at 37 degrees Celsius. (Biotin-antibody (1x) may seem foggy due to the presence of biotin. Bring the solution up to room temperature and gently stir until it seems homogeneous in color).
5. Aspirate and wash each well, repeating the procedure twice more for a total of three washes. Use a squirt bottle, multi-channel pipette, manifold dispenser, or autowasher to fill each well with Wash Buffer (200L). Allow the wells to stand for 2 minutes after each filling. Complete removal of liquid at each phase is critical for excellent performance. After the final wash, aspirate or decant any residual wash Buffer to ensure that it is no longer present. Invert the plate and wipe it with a clean paper towel to remove the grease.

6. Pour 100 microliters of HRP-avidin (1x) into each well. Replace the adhesive strip on the microtiter plate with a fresh one. Incubate for 1 hour at 37 degrees Celsius.
7. As in step 6, repeat the aspiration/wash procedure five times more.
8. Fill each well halfway with 90 mL of TMB Substrate. Incubate for 15-30 minutes at a temperature of 10 37°C. Keep away from direct sunlight.
9. Divide the Stop Solution evenly among the wells, carefully tapping each well to achieve complete mixing.

3.2.3 Calcium assay kit (Colorimetric) ab102505

Calcium is required for the survival of all living species, and its sequestration and release into and out of the cytoplasm serves as a signal for a variety of cellular activities throughout the body. Calcium is present in bones and teeth to a greater extent than everywhere else in the body, with the remaining one percent found in the blood and soft tissue. The concentration of calcium in the blood is strictly regulated (8.4-11.4 mg/dL), and any deviation from this range might have catastrophic consequences. Among other things, calcium aids in the constriction and relaxation of blood vessels as well as the transmission of nerve impulses as well as muscle contraction and hormone release. Calcium ion channels regulate the movement of calcium ions across cell membranes, allowing them to regulate the activation and inhibition of a broad range of enzymes in the process. Low calcium levels may be caused by a variety of factors, including chronic renal failure, vitamin D insufficiency, and low magnesium levels in the blood, which can occur in severe alcoholism.

Product name: Calcium Assay Kit (Colorimetric)
Sample type: Urine, Serum, Plasma, Other biological fluids, Tissue Extracts, Cell Lysate
Assay type: Quantitative
Sensitivity: > 0.1 mM
Range: 0.1 mM - 25 mM
Assay time: 0h 20m
Species reactivity Reacts with: Mammals, Other species

Product overview: Calcium Assay Kit (Colorimetric) ab102505 provides a simple assay to determine calcium concentration within the physiological range of 0.4 – 100 mg/dL (0.1 – 25 mM). In the calcium assay protocol, a chromogenic complex is formed between calcium ions and 0- cresolphthalein. The complex is measured at OD = 575 nm.

3.3 Statisitic Analysis

ANOVA one way test were conducted for all biochemical paramaters using the SPSS program, version 23. It was also using the same program to find the correlation between the biochemical paramaters in our study.

4. RESULTS AND DISCUSSION

In our study, 130 subjects (65 Women with thalassemia and 65 without thalassemia) with varying degrees of disease activity matched for age, sex and body mass index will be evaluated. The tests listed below was be carried out in accordance with the modus operandi (kit user manual) specified by the manufacturing company. The Tests are: PTH, CBC, Ca, RBS, and total cholesterol, HDL, LDL, VLDL and PTH/Hb. The results of mean age, sex and body mass index and some others parameters such as PTH, CBC, Ca, RBS, total cholesterol, HDL, LDL, VLDL and PTH/Hb are shown in Table 4.1, the correlation between PTH and other parameters study are shown in Table 4.2.

Table 4.1 The result means of study parameters

Test	Group A Mean ± SD (65)	Group B Mean ± SD (65)	Total Means of group	P-Value
Age (year)	23.75 ± 4.287	21.00 ± 3.789	22.37 ±4.199	0.110
PTH (Pg/mL)	40.30 ± 4.818	50.00 ± 8.090	45.15 ± 8.179	0.002
Ca (mg/dL)	9.105 ± 0.927	7.862 ± 1.130	8.483 ± 1.193	0.008
WBC	7.300 ± 2.163	14.17 ± 3.510	10.73 ± 4.525	0.001
Hb(g/dL)	12.36 ± 1.346	8.513 ± 1.493	10.43 ± 2.407	0.010
Platelete	292.00 ± 73.193	162.66± 41.60	227.33 ± 88.05	0.001
RBS (mg/dL)	93.00 ± 13.300	89.58 ± 13.83	91.291 ± 13.38	0.544
Tc (mg/dL)	217.16 ± 43.73	155.16 ± 26.13	186.16 ± 47.37	0.002
Tg (mg/dL)	94.50 ± 23.63	92.41 ± 11.50	94.50 ± 23.63	0.786
HDL (mg/dL)	50.91 ± 7.763	41.83 ± 7.321	46.37 ± 8.716	0.007
LDL (mg/dL)	117.79 ± 21.681	92.20 ± 20.77	104.99 ± 24.53	0.016
VLDL	18.90 ± 4.727	18.48 ± 2.300	18.69 ± 3.642	0.674
PTH/Hb (%)	3.311 ± 0.620	6.030 ± 1.352	4.671 ± 1.728	0.001

Table 4.2 Correlation between PTH and other parameters study

Teast	No	P-Value
PTH - Age	0.401	P > 0.05
PTH - Ca	0.388	P > 0.05
PTH - WBC	0.493*	P < 0.05
PTH - Hb	0.527**	P < 0.05
PTH - Platelete	0.337	P > 0.05
PTH - RBS	0.330	P > 0.05
PTH - Tc	0.514*	P < 0.05
PTH - Tg	0.144	P > 0.05
PTH - HDL	0.087	P > 0.05
PTH - LDL	0.475	P > 0.05
PTH - VLDL	0.144	P > 0.05
PTH - PPTH/Hb	0.789**	P < 0.05

4.1 Age and RBS

The results of the study showed that there were no statistical differences between the average age and RBS in thalassemia when comparing the results to the control group, and the results of the control group, patients and the total number were as follows (Age, 23.75 ± 4.287, 21.00 ± 3.789, 22.37 ± 4.199, and RBS, 93.00 ± 13.30, 89.58 ± 13.83, 91.291 ± 13.38 respectively), as shown in Table 4.1 and Figure 4.1.

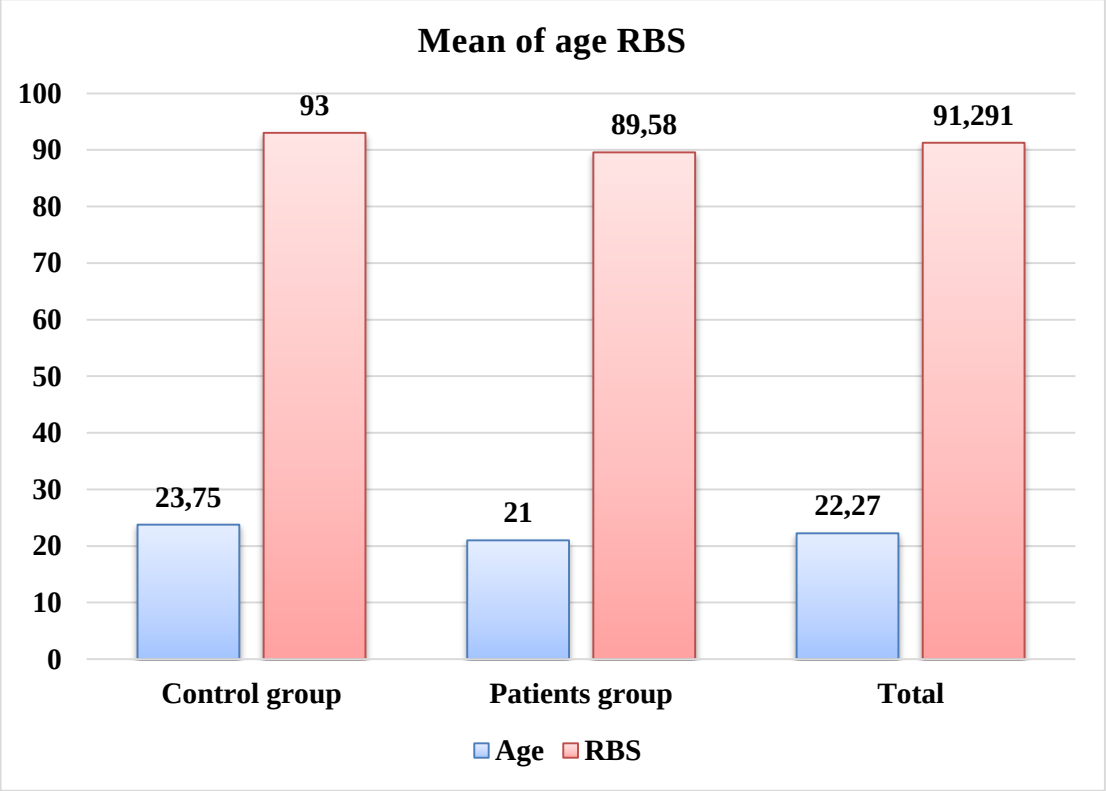

Figure 4.1 The means of age and RBS compared to control group and total

4.2 PTH and Calcium

The results of the present study in relation to parathyroid hormone and calcıum also indicated that there were statistical differences between the averages of parathyroid hormone andcalcıum in thalassemia when comparing the results to the control group, and the results of the control group, patients and the total number were as follows (PTH, 40.30

± 4.818, 50.00 ± 8.090, 45.15 ± 8.179 and Ca, 9.105 ± 0.927, 7.862 ± 1.130, 8.483 ± 1.193 respectively), as shown in Table 4.1 and Figure 4.2.

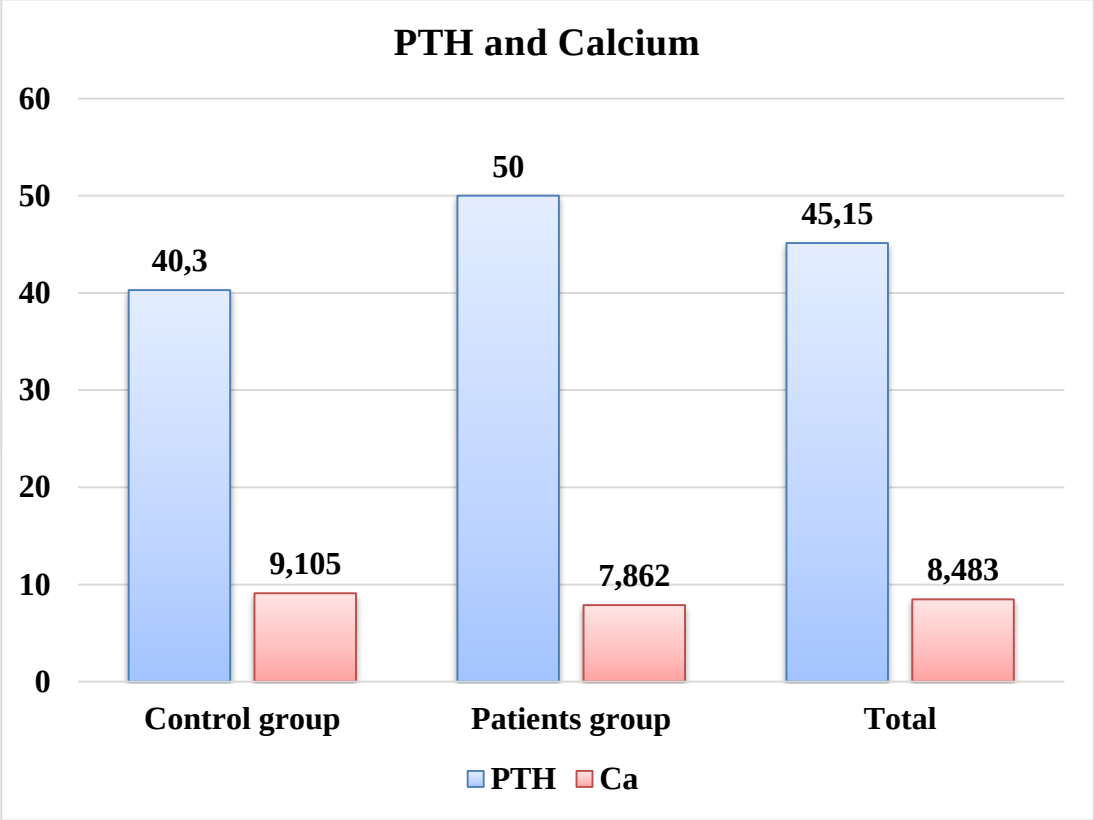

Figure 4.2 The means of PTH and Ca compared to control group and total

4.3 WBC, Hb and Platelete

Also, the results of the study for WBC, Hb and Platelet indicate that there are high statistical differences between the averages of WBC, Hb and Platelet in thalassemia when comparing the results to the control group, which indicates the strong effect on blood components, where thalassemia is one of the most famous blood diseases. The results of the control group, patients and the total number were as follows (WBC, 7.300 ± 2.163, 14.17 ± 3.510, 10.73 ± 4.525 and Hb, 12.36 ± 1.346, 8.513 ± 1.493, 10.43 ± 2.407 and 292.00 ± 73.193, 162.66± 41.60, 227.33 ± 88.05 respectively), as shown in Table 4.1 and Figure 4.3, the means of platelet compared to control group and total are shown in Figure 4.4.

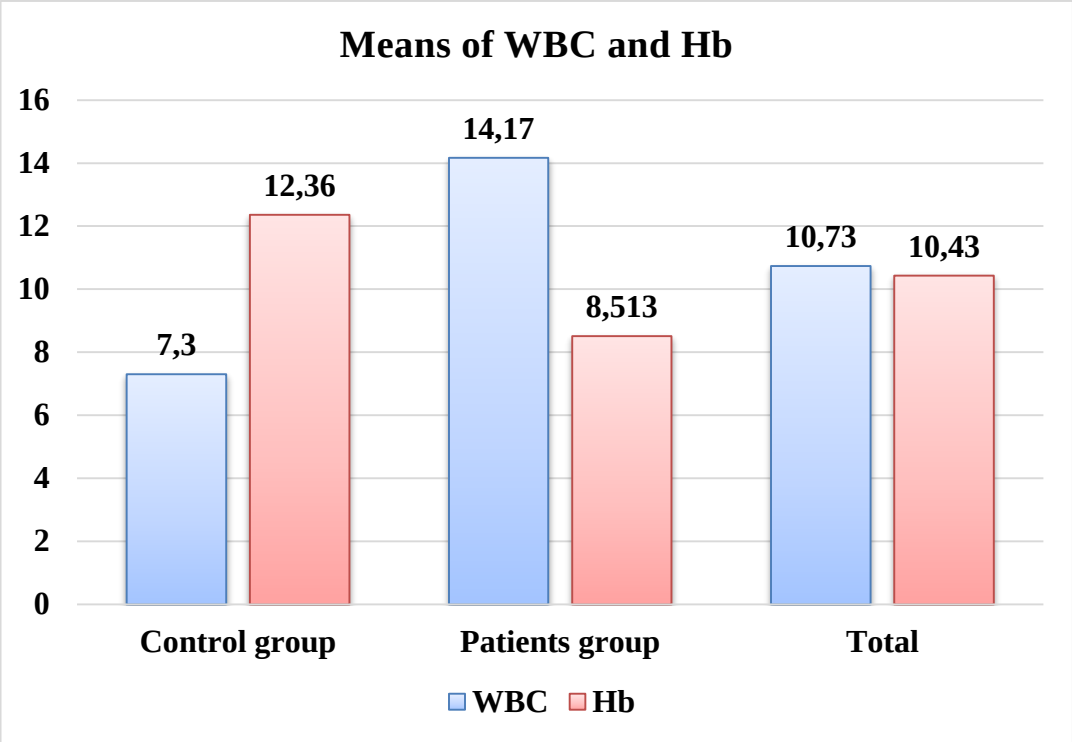

Figure 4.3 The means of WBC and Hb compared to control group and total

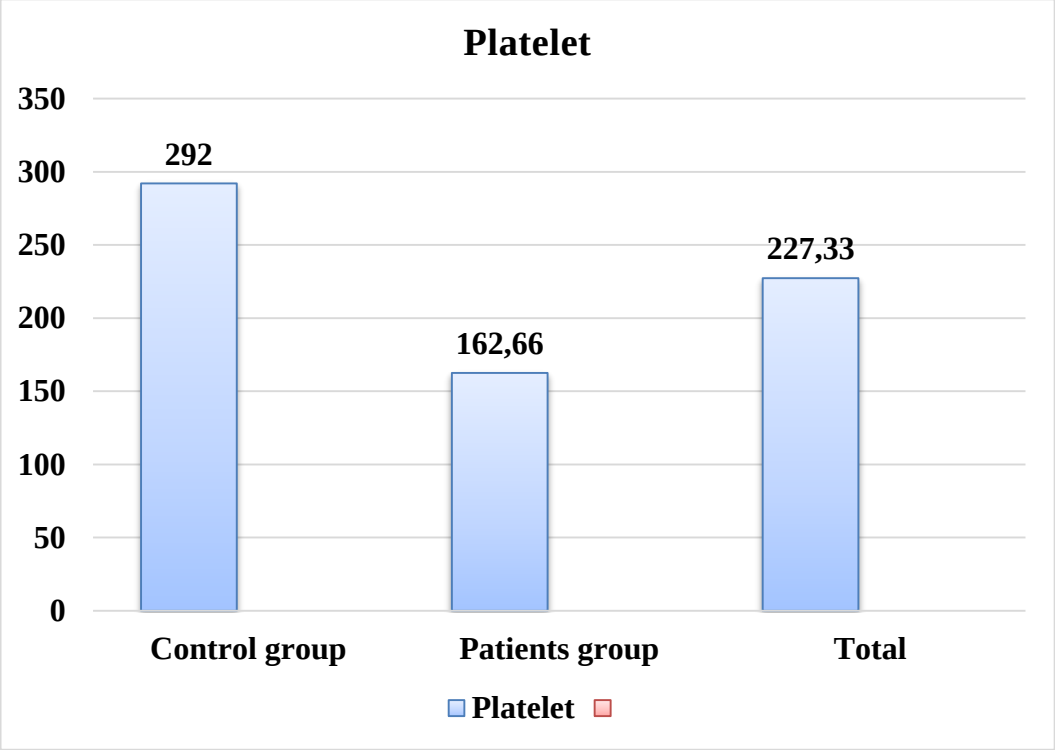

Figure 4.4 The means of platelet compared to control group and total

4.4 Lipid Profile

The results of the study lipid profile indicated that there were high statistical differences between the averages of total cholestrol, LDL and HDL (Control group, 217.16 ± 43.73, 117.79 ± 21.681, 50.91 ± 7.763 and patients group, 155.16 ± 26.13, 41.83 ± 7.321, 92.20 ± 20.77 respectively) in thalassemia when comparing the results to the control group, which indicates the effect and the increase in its percentage. While there were no statistically significant differences for triglycerides and VLDL (Control group, 94.50 ± 23.63, 18.90 ± 4.727 and patients group, 92.41 ± 11.50, 18.48 ± 2.300 respectively), as shown in Table 4.1 and Figure 4.5.

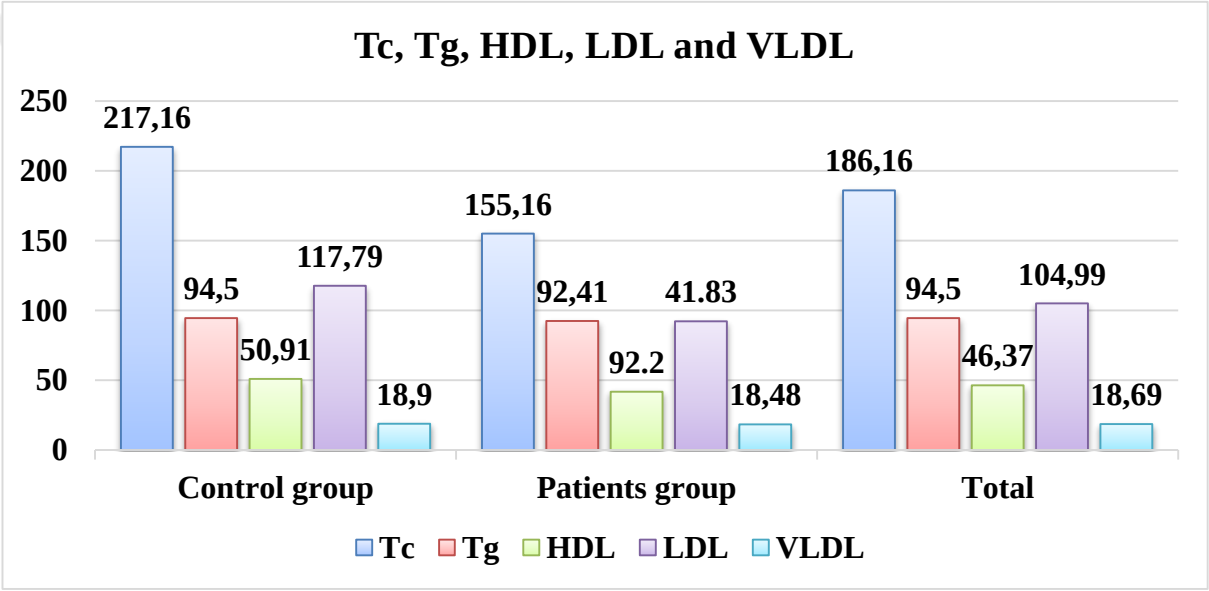

Figure 4.5 The means of lipid profile compared to control group and total

4.5 PTH/ Hb

In our study, we took the percentage of PTH/Hb in order to know the importance of this percentage in the diagnosis, and the results of the study indicated the presence of high statistical differences between the PTH/Hb (3.311 ± 0.620, 6.030 ± 1.352, 4.671 ± 1.728, respectively) and thalassemia when comparing the results to the control group, which

indicates the effect and the increase in its percentage. As shown in Table 4.1 and Figure 4.6.

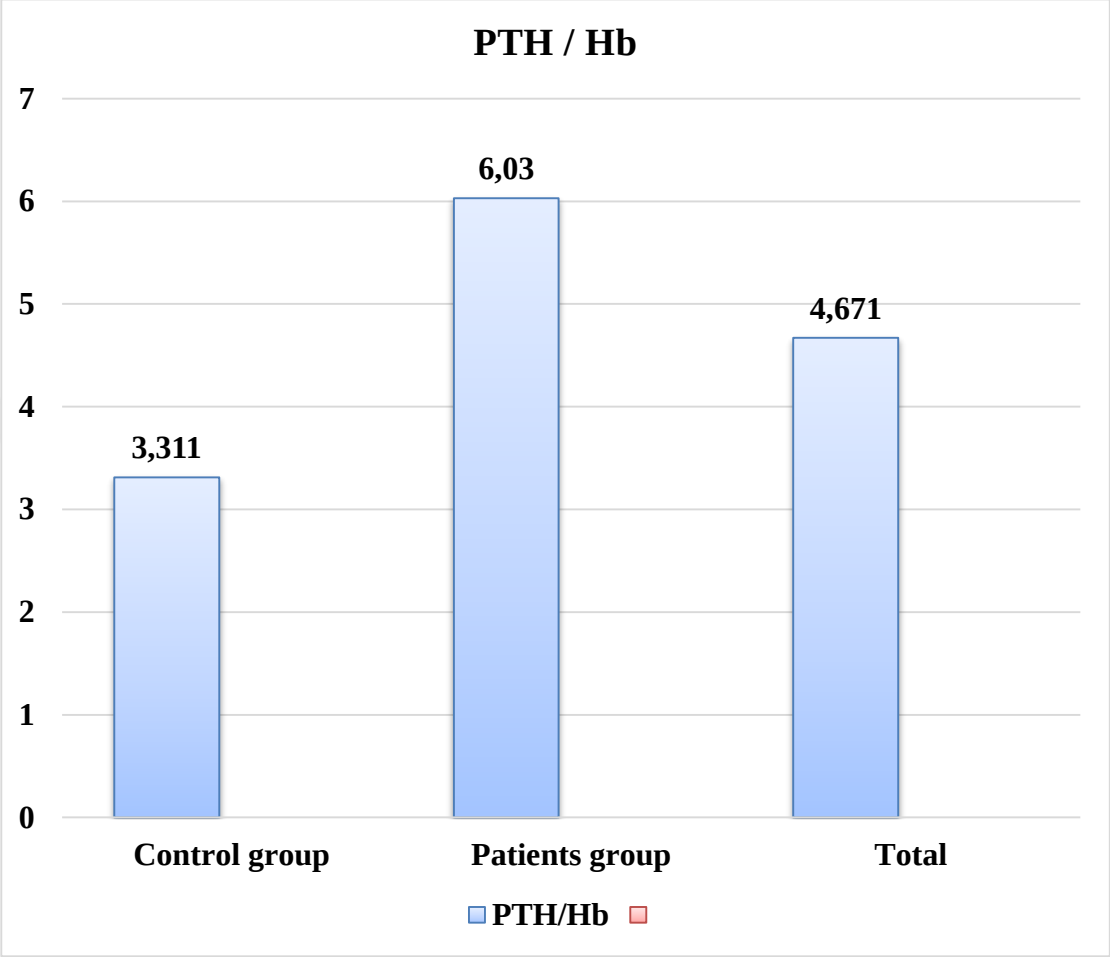

Figure 4.6 The means of PTH/Hb compared to control group and total

5. CONCLUSIONS AND RECOMMENDATION

Thalassemia is one of the diseases that spread in Iraq, especially in the center and south, which prompted us to research some tests that are related to the disease or that increase the speed of diagnosis of the disease. The results of our study with respect to age and random blood sugar percentage indicate that there is no statistical significance in diagnosing the disease, but age remains related to the development of the disease. Also, there was no correlation between age and parathyroid hormone when Pearson's test was performed. Also, there was no statistical significance for triglycerides and very low-density lipoprotein. On the contrary, there is great importance for the test of parathyroid hormone and lipids, and it may have a great role in diagnosing the disease or a little deterioration of the patient's condition. There was correlation between WBC, Hb, total cholesterol and PTH/Hb and parathyroid hormone when Pearson's test was performed.

The study of Ansari-Moghaddam and his team indicated relatively high survival rates in thalassemia patients. Patient survival was unfavorable in poorer areas. Factors including a woman's gender, level of higher education, marriage, and living in major cities reduced the risk of death at younger ages and improved survival (Ansari-Moghaddam *et al.* 2018). Thyroid dysfunction, according to reports in the literature, is associated with iron overload, which often arises in the second or third decade of life in individuals with thalassemia major. The findings of our study, however, indicate that iron overload PTH can develop in a significant number of patients with thalassemia major. As a result, all thalassemia cases should be carefully monitored for endocrine organ function, such as hyperparathyroidism, even in the first decade of thalassemia major patients (Pirinççioğlu and Söker 2017).

A substantial drop in blood PTH, serum calcium concentrations was reported for patients although alkaline phosphatase, phosphorous and albumin-corrected calcium levels did not alter significantly when compared with the relevant mean values for the control group. Vitamin D and calcium supplementation led to a considerable rise in parathyroid hormone and blood calcium levels. The supplement also increases the excretion of calcium in the urine. The researchers came to the conclusion that thalassemia patients suffer from or develop hypoparathyroidism, which results in decreased blood calcium concentrations, which may be remedied by taking vitamin D and calcium supplements (Goyal *et al.*

2010). Identify patients who have a limited secretion capacity of the parathyroid gland that is associated with their biochemical categorization. Before it may be used in clinical practice to evaluate parathyroid dysfunction, it must first undergo clinical validation (Majid *et al.* 2019). Hypoparathyroidism was discovered in 18 percent of the individuals with thalassemia, growth retardation/short stature was discovered in 93 percent of the patients, and weight loss was discovered in 93 percent of the patients. Mean age at diagnosis was 12.6 years (range 11-16 years), mean serum calcium level was 7.53 mg/dL (range 7.58 - 9.04 mg/dL), mean serum ferritin level was 5831.0 ng/mL (range 2000 - 8,064 ng/dL), and mean serum phosphate level was 5.63 mg/dL (range 4.50 - 7.73 mg/dL) at the time of diagnosis. In the same research, the majority of patients had low levels of the hormone parathyroid hormone (PTH). In addition, we observed low height in the majority of the patients, although it was determined to be normal in the comparison group. Patients with beta thalassemia have been shown to have hypoparathyroidism (HPT) together with growth retardation (p 0.001). An increase in both serum phosphorous and alkaline phosphatase levels was reported in patients when compared to controls, indicating that the cases were suffering from a substantial calcium deficiency (Manne *et al.* 2020).

5.1 Recommendations

1- Increasing the number of selected groups as well as increasing the number of samples to reduce the standard deviation.
2- Conducting more studies for the rest of the Iraqi governorates and comparing them with the current study to show the impact of urbanization and the nature and type of nutrition on this type of disease.
3- Increasing the type of tests to find out other, more reliable methods of diagnosing this kind of diseases

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