A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF ÇANKIRI KARATEKİN UNIVERSITY

THE RELATION BETWEEN SERUM GLUCOSE AND INSULIN WITH HYPOTHYROIDISM IN MIDDLE AGED WOMEN

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

BY

MARWAN SAMI ABDULHUSSEIN AL-TAMEEMI

ÇANKIRI

2021

THE RELATION BETWEEN SERUM GLUCOSE AND INSULIN WITH HYPOTHYROIDISM IN MIDDLE AGED WOMEN

By Marwan Sami Abdulhussein AL-TAMEEMI

December 2021

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

Advisor **:** Assoc. Prof. Dr. Saliha ALYAR
Co-Advisor **:** Prof. Dr. Zina Farouk FOUAD

Examining Committee Members:

Chairman **:** Asst. Prof. Dr. Melike BİLGİ KAMAÇ
Chemistry
Çankırı Karatekin University

Member **:** Asst. Prof. Dr. Fatma HAMURCU
Biology
Bartın University

Member **:** Assoc. Prof. Dr. Saliha ALYAR
Chemistry
Çankırı Karatekin University

Approved for the Graduate School of Natural and Applied Sciences

Prof. Dr. İbrahim ÇİFTÇİ
Director of Graduate School

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Marwan Sami Abdulhussein AL-TAMEEMI

ABSTRACT

THE RELATION BETWEEN SERUM GLUCOSE AND INSULIN WITH HYPOTHYROIDISM IN MIDDLE AGED WOMEN

Marwan Sami Abdulhussein AL-TAMEEMI
Master of Science in Chemistry
Advisor: Assoc. Prof. Dr. Saliha ALYAR
Co-Advisor: Prof. Dr. Zina Farouk FOUAD
December 2021

The most common endocrine disorders in the general population are diabetes and thyroid disorders. In hypothyroidism, glucose metabolism is affected by a variety of mechanisms, including impaired genetic expression of genes, overproduction of hepatic glucose output, and increased absorption of splanchnic glucose, with physiological abnormalities leading to impaired glucose utilization and excretion in muscles. Hypothyroidism is at least twice as common in women as in men. Although hypothyroidism is most common in middle-aged or older women, the disease can occur at any age. In this study, middle-aged women (aged 45-65 years) were selected, who were previously diagnosed with hypothyroidism and did not have other chronic diseases. This study investigated the incidence of T1DM and T2DM in patients with pre-existing hypothyroidism and determined the incidence of hypothyroidism with pre-existing T1DM and T2DM. It has been observed that female patients between the ages of 45 and 65 who were diagnosed with hypothyroidism have a risk of developing diabetes. The risk of developing hypothyroidism in female patients aged 45–65 years diagnosed with diabetes was evaluated as positive based on the results of two of the three markers.

2021, 67 pages

Keywords: Hypothyroidism, Diabetes mellitus, T1DM, T2DM

ÖZET

ORTA YAŞLI KADINLARDA SERUM GLİKOZ VE İNSÜLİN ARASINDAKİ HİPOTİROİDİZM İLİŞKİSİ

Marwan Sami Abdulhussein AL-TAMEEMI
Kimya, Yüksek Lisans
Tez Danışmanı: Doç. Dr. Saliha ALYAR
Eş Danışman: Prof. Dr. Zina Farouk FOUAD
Aralık 2021

Genel popülasyonda görülen en yaygın endokrin bozukluklar diyabet ve tiroid bozukluklarıdır. Hipotiroidizmde, glikoz metabolizması, kaslarda bozulmuş glikoz kullanımına ve atılmasına yol açan fizyolojik anormalliklerle genlerin bozuk genetik ekspresyonu, hepatik glikoz çıkışının aşırı üretimi ve splanknik glikozun artmış emilimi gibi çeşitli mekanizmalardan etkilenir. Tiroid bozuklukları arasında hipotiroidizm dünya çapında en yaygın olanıdır. Genellikle tip 1 diabetes mellitus T1DM ve T2DM ile birlikte var olduğu bulunmuştur. Hipotiroidizm en çok orta yaşlı veya yaşlı kadınlarda görülmesine rağmen, hastalık her yaşta ortaya çıkabilir. Bu çalışmada orta yaşlı kadınlar (45-65 yaş arası) seçilmiş, daha önce hipotiroidizm teşhisi konulmuş ve başka kronik hastalıkları bulunmayan kişilerden oluşmuştur. Bu çalışma ile önceden mevcut olan hipotiroidizm hastalarında T1DM ve T2DM insidansını araştılmış ve önceden var olan T1DM ve T2DM ile hipotiroidizm insidansını belirlenmiştir. Hipotiroidizm tanısı alan 45–65 yaş aralığındaki kadın hastaların diyabet geliştirme riskinin olduğu görülmüştür. Diyabet tanısı alan 45–65 yaş aralığındaki kadın hastaların hipotiroidizm geliştirme riskinin olduğu üç belirteçten ikisinin sonucuna dayanarak müspet olarak değerlendirilmiştir. Bu çalışmanın amacı; orta yaşlı kadınlarda hipotiroidizm ve kan şekeri düzeyleri arasındaki ilişkiyi belirlemektedir.

2021, 67 sayfa

Anahtar Kelimeler: Hipotiroidizm, Diabetes mellitus, T1DM, T2DM

PREFACE AND ACKNOWLEDGEMENTS

I would like to thank my thesis advisor, Assoc. Prof. Dr. Saliha ALYAR, for his patience, guidance and understanding.

To my dear mother and father, to my wife and children, to everyone who stood with me and supported me in my thesis, and to everyone who wished me well. And to my dear brothers. Finally, to my Prof. Dr. Zina Farouk FOUAD for her continuous support and support.

Dedicate this success to them.

Marwan Sami Abdullhussein AL-TAMEEMI

Çankırı-2021

CONTENTS

LIST OF ABBREVIATIONS

AITD	Autoimmune thyroid dysfunction a
AMPK	5' Adenosine monophosphate activated protein kinase
DM	Diabetes mellitus
FPG	Fasting plasma glucose
FT3	Free triiodothyronine
FT4	Free thyroxine
GLP-1	Glucagon-like peptide-1
GLUT 2	Glucose transporter type 2 gene
GLUT 5	Glucose transporter 5
HbA1c	Hemoglobin A1c
NE	Norepinephrine
PC	Pyruvate carboxylase
PEPCK	Phosphoenol pyruvate kinase
PGC-1 alfa	PPAR gamma coactivator-1 alpha
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid stimulating hormone

LIST OF FIGURES

LIST OF TABLES

1. INTRODUCTION

The most common endocrine disorders in the general population are diabetes and thyroid disorders. These two disorders are mutually related and affect each other. In hypothyroidism, glucose metabolism is affected by a variety of mechanisms, including impaired genetic expression of genes, overproduction of hepatic glucose output, and increased absorption of splanchnic glucose, with physiological abnormalities leading to impaired glucose utilization and excretion in muscles. Thus, it predisposes to diabetes mellitus. It is well known that hyper- and hypothyroidisms are associated with insulin resistance and are the main cause of impaired glucose metabolism in type-2 diabetes mellitus (T2DM) and worsen glycemic control (Hage *et al.* 2011, Wang 2013).

Among thyroid disorders, hypothyroidism is the most common worldwide. It has often been found to coexist with type 1 diabetes mellitus (T1DM) and T2DM. It is thought to be a triggering factor for hypoglycemia in diabetic patients. In addition, the incidence of hypothyroidism increases with age and is more common in women (Kalra *et al.* 2014, Saluja *et al.* 2018).

The prevalence of T2DM in the diabetes mellitus population (about 90%) is higher compared to T1DM (about 10%) due to a sedentary lifestyle and increase in obesity. Also, the incidence of hypothyroidism is higher in T2DM patients than in T1DM patients. It is well known that thyroid hormones are insulin antagonists. Insulin has been found to inhibit the conversion of thyroxine (T4) to triiodothyronine (T3); therefore, hypothyroidism is demonstrated in diabetic patients with significantly lower serum T3 and T4 levels than in diabetic subjects without hypothyroidism. In addition, in a study, diabetic hypothyroid patients using metformin showed a decrease in thyroid stimulating hormone (TSH) levels at the baseline level after 6 months. This shows the relationship between antidiabetic treatment and the risk of hypothyroidism (Mouradian and Abourizk 1983, Ozair *et al.* 2018).

Hypothyroidism, or underactive thyroid, occurs when the thyroid gland is unable to secrete as much thyroxine (T4) as the body needs. Because T4 regulates essential functions such as heart rate, digestion, physical growth, and mental development, malnutrition of this hormone can slow life-sustaining processes, damage organs and tissues throughout the body, and lead to life-threatening complications.

Hypothyroidism is at least twice as common in women as in men. Although hypothyroidism is most common in middle-aged or older women, the disease can occur at any age.

It is not unusual for someone to have both hypothyroidism and diabetes, hypothyroidism increases the risk of developing type 2 diabetes.

Several mechanisms may explain the association between low thyroid function and diabetes risk:

- Decreased insulin sensitivity.
- Tolerance of blood sugar due to reduced ability of insulin to increase glucose utilization primarily in muscle.
- Down-regulation of plasma membrane glucose transporters.

The aim of this study; determines the relationship between hypothyroidism and blood sugar levels in middle-aged women. With this study, we aim to shed light on future studies.

2. GENERAL INFORMATION

Thyroid; It is a butterfly-shaped gland in your throat, just above your collarbone. It is one of the endocrine glands that secrete hormones. Thyroid hormone determines the rate of many activities in your body. For example, how fast you burn calories or how fast your heart beats. All these activities are your body's metabolism. If your thyroid is overactive, the thyroid gland secretes more thyroid hormone than your body needs. This is called hyperthyroidism (Coller and Huggins 1927).

Thyroid diseases and diabetes mellitus (DM) are two common diseases in our society. Although it differs according to the geographical region, urban-rural area, age group and gender, DM is generally seen at the rate of 6 - 8%, type 2 DM is responsible for approximately 90% of this rate. The epidemiology of thyroid diseases depends on the criteria chosen when making the diagnosis. In some studies, evaluation is made according to pathological diagnoses, while in others imaging and laboratory analyzes are included. Therefore, the methods used for diagnosis in epidemiological studies are important. In general, as a result of these studies, it can be said that the social frequency of thyroid diseases is approximately 7% (Goglia *et al.* 1999, Holl *et al.* 1999, Barker *et al.* 2005, Brenta *et al.* 2007, Kordonouri *et al.* 2009, Kadiyala *et al.* 2010).

Type 2 DM is a chronic metabolic disease characterized by the presence of hyperinsulinemia and/or insulin resistance, usually in advanced ages, on the basis of obesity. Basedow Graves' disease and Hashimoto's disease, which are frequently encountered thyroid diseases, develop on an autoimmune basis. This is followed by toxic multinodular goiter (MNG), toxic solitary adenoma and subacute thyroiditis, respectively. In addition, the frequency of thyroid diseases varies according to the status of regional iodine intake. In areas where iodine intake is sufficient, hypothyroidism is most commonly due to chronic autoimmune thyroiditis (atrophic autoimmune thyroiditis and Hashimoto's thyroiditis) and radioactive iodine ablation or surgery. Hypothyroidism is common in iodine-deficient regions due to insufficient hormone production.

Information about Diabetes Mellitus goes back to the years before Christ. A disease characterized by excessive urination was described in Egyptian papyri around 1500 before Christ. In the 5th century, the Indian physician Susruta, in his work called “Susruta-Samhita”, talked about a disease characterized by excessive thirst, a heavy bad breath, tiredness and honey urine. The disease was first named diabetes by Aretheaus of Cappadocia, who lived between 130-200 before Christ. Aretheaus in his work, diabetes, “disease is the watering of the flesh and limbs into urine. The patient with this disease is never tempted to drink water, he can never stop himself from urinating because the fluids flow out of his body (diabetes: straining, straining), kidneys, bladder, urinary tract is like a wide opened channel. After a while, this situation causes weakening and collapse, life only lasts for a while, it doesn't last very long (Baxter *et al*. 2001, Baxter and Webb 2009).

2.1 Epidemiology

The thyroid gland plays a very important role in the human body, it controls many activities and provides the production of hormones. The thyroid gland is just one of the endocrine glands. Knowing the 13 symptoms in this article is essential for diagnosing a thyroid disorder. Those with one of these symptoms should have their blood thyroid hormone level measured and see a doctor. There are many thyroid diseases and disorders, but 2 of them are very common; hyperthyroidism (producing more thyroid hormone than necessary) and hypothyroidism (producing less thyroid hormone than necessary). Other conditions are goiter (enlargement of the thyroid gland), thyroid cancer, thyroid nodules and thyroiditis (inflammation of the thyroid gland). Hypothyroidism is more common than hyperthyroidism, and although these two conditions are closely linked, there are many important differences in their diagnosis and treatment (Tunbridge *et al.* 1977, Hollowell *et al.* 2002).

It has been known for years that thyroid hormone affects the heart and systemic circulation. Thyroid hormone increases oxygen consumption and thermogenesis, and accelerates the breakdown of low-density lipoprotein (LDL) cholesterol. Triiodothyronine (T3) increases myositis contractility in the myocardium. It accelerates the heart by changing depolarization and repolarization in the sinoatrial node in the conduction system of the heart.

The prevalence of thyroid disorder in the diabetic population was reported as 13.4%, higher prevalence (31.4%) in female T2DM patients and (6.9%) in male T2DM patients. The prevalence of thyroid dysfunction in T2DM patients was reported by Akbar and his team as 12.3% in Greece and 16% in Saudi Arabia (Akbar *et al.* 2006). T2DM patients are more prone to thyroid disorders (Akbar *et al*. 2006). T2DM hastaları tiroit bozukluklarına daha yatkındır.

2.2 Peripheral Effects of Thyroid Hormones on Insulin

The thyroid gland is an endocrine organ that regulates normal growth, development and metabolism, energy and heat production. It plays a role in growth and development by affecting oxygen consumption, protein, carbohydrate and vitamin metabolism, and its effects on metabolism continue in adulthood. It is known that thyroid hormones have both stimulant and regulatory effects on carbohydrate metabolism. Recently, the relationship between insulin and thyroid hormones, which have an effect on glucose metabolism, has also attracted attention. Among them is its effect on insulin secretion. Thyroid diseases affect 6-8% of adults in the world and 8.9% in the USA (Stanická *et al.* 2005, Mitrou *et al*. 2010).

2.2.1 Thyrotoxicosis

Thyroid storm is a life-threatening form of thyrotoxicosis that usually occurs after an initiating event. The most common trigger is infection or sepsis. Patients habitually have a history of thyrotoxicosis, but thyroid storm may be the first clinical presentation. Untreated thyroid storm is almost always fatal. Treatment improves thyroid storm outcomes, but mortality is between 20% and 50%. Mental status change is the most prominent feature. Changes such as agitation, emotional lability, delirium, convulsions, and chorea-like abnormal movements are seen. Patients may also have autonomic dysfunction summarized by excessive diaphoresis, severe hyperthermia, hypertension, and persistent rhythm disturbances (Eledrisi *et al*. 2006, Potenza *et al*. 2009), this event is illustrated in Figure 2.1.

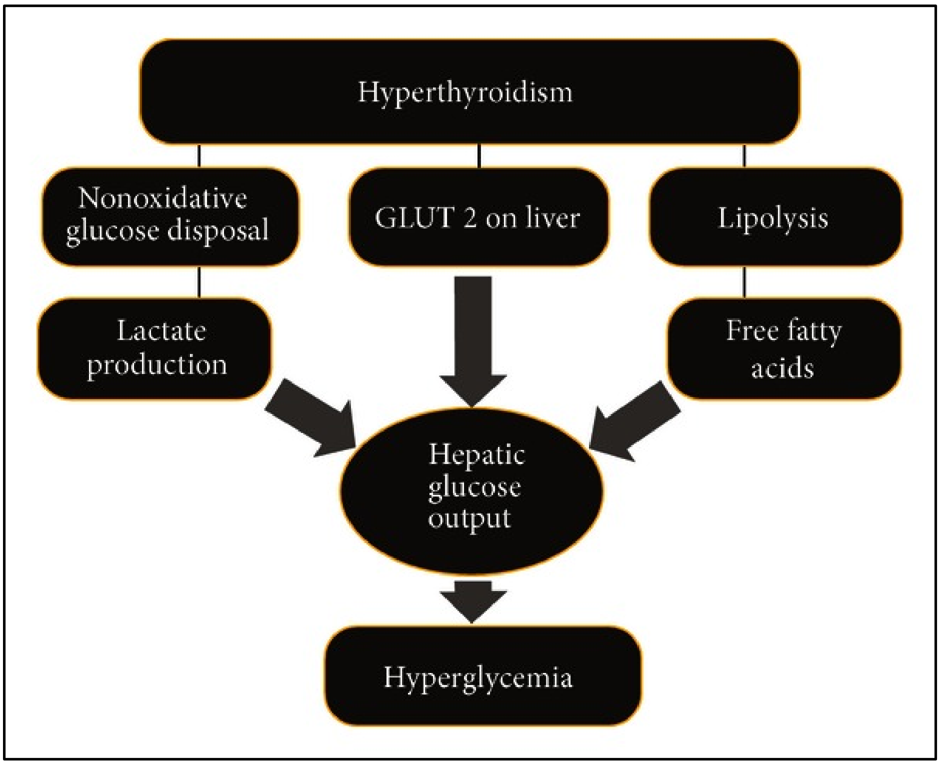

Figure 2.1 The relationship between hyperthyroidism and hyperglycemia through limetabolism, oxidative stress and hepatis dysfunction (Eledrisi *et al.* 2006, Potenza *et al.* 2009)

2.2.2 Hypothyroidism

Underactive thyroid is called "hypothyroidism". Common symptoms of hypothyroidism include weakness, fatigue, difficulty concentrating, constipation, chills, and intolerance to cold. Dry skin, coarsening of the skin, and changes in color that turn orange, which are sometimes thought to be caused by dermatological diseases, may also develop due to under-functioning of the thyroid gland. In this case, it would be beneficial to consult an endocrinologist.

Whether the thyroid gland works adequately or not is determined by the values of the "TSH hormone" secreted from the part of the brain called the "pituitary". TSH stimulates the hormone-producing structures in the thyroid gland, allowing it to be produced and mixed with the blood. When the thyroid gland works less than normal, the delivery of TSH from the pituitary to the blood increases. When the required amount of thyroid hormone cannot be secreted, a condition called hypothyroidism occurs and enough thyroid hormone cannot be secreted into the tissues, and the metabolism naturally slows down. Hypothyroidism can cause retardation in growth and development in infants and children. If treatment is delayed, the chance of recovery of mental retardation caused by hypothyroidism decreases. In adults, there is a general slowdown in the body and metabolism. However, the symptoms of hypothyroidism in adults improve to a great extent with thyroid hormone treatment (Duntas *et al*. 2011), this event is illustrated in Figure 2.2.

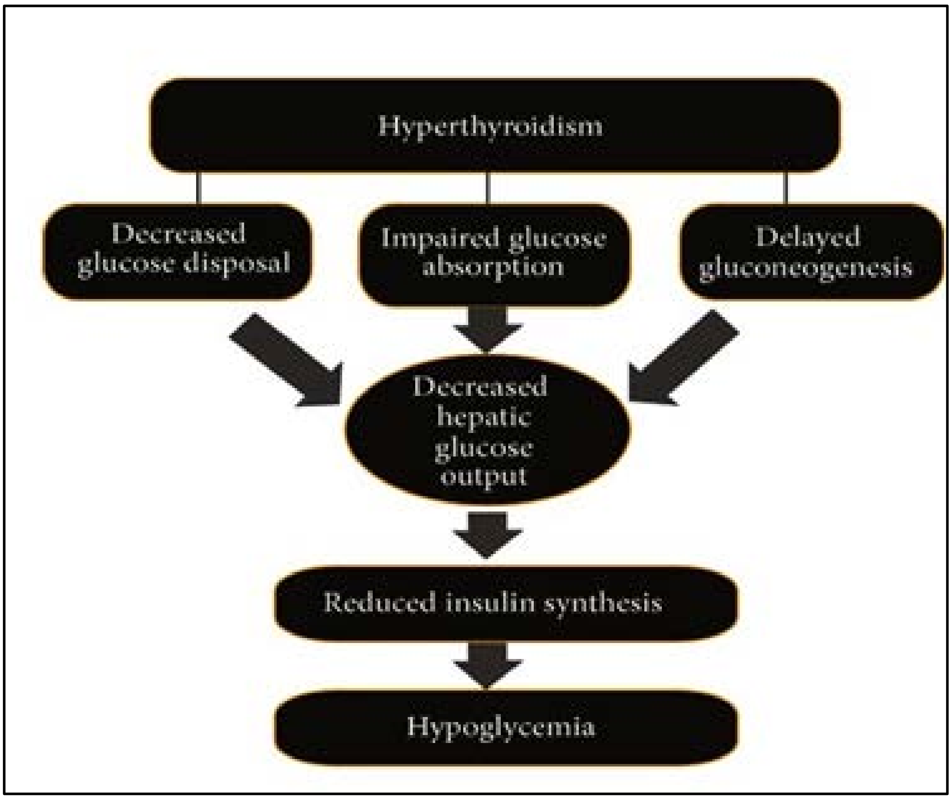

Figure 2.2 The relationship between hypothyroidism and hypoglycemia mediated by decreased insulin synthesıs and umpaired hepatic glucose output (Duntas *et al*. 2011)

2.3 The Relationship Between Hyperthyroidism and T2DM

2.3.1 The role of insulin resistance and other factors

Insulin resistance; It is defined as a decreased response to normal concentrations of circulating insulin. Insulin resistance can be seen in obese, non-diabetic and type 2 diabetic individuals. The pathophysiological reasons underlying insulin resistance have not been adequately clarified. Insulin activity defect is generally seen under insulin resistance. Measurement of insulin resistance in routine clinical evaluation can be done with the euglycemic insulin clamp method, thus indirectly assessing insulin function. Insulin resistance has a broad spectrum. In the clinical picture, different pictures can be seen from normal glycemic values and increased insulin level to hyperglycemia despite increased insulin, in this case the patient will be considered as a metabolic syndrome patient (Randin *et al*. 1985, DeFronzo 2004, Muoio and Newgard 2008, Dimitriadis *et al*. 2008, Brenta *et al*. 2009).

Insulin resistance syndrome or syndrome X with different names, metabolic syndrome is a combination of clinical and laboratory findings to be counted. Insulin resistance, hyperinsulinemia, obesity, dyslipidemia, and hypertension can be seen together, and in this case, the patient will be considered as a metabolic syndrome patient. Therefore, patients with insulin resistance should be evaluated in terms of metabolic syndrome. The metabolic syndrome and its components will be examined in more detail later. Various mutations of insulin receptor-related genes have been identified. Insulin receptor gene mutation is rare, but the frequency of insulin resistance has increased in patients with mutations. Mutations in genes such as Glut 4 and glycogen synthase have also been found to be associated with the development of insulin resistance and type 2 diabetes (DeFronzo *et al.* 1985, Mari *et al.* 1994, Mandarino *et al.* 2001).

In insulin resistance, abnormalities in the concentration, affinity, or both of the insulin receptor impair the effectiveness of insulin. 'Down Regulation'; It defines the decrease in the number of insulin receptors elicited by persistently elevated insulin in the circulation. Presumably, increased degradation of insulin in the cell also accompanies this picture.

However, the insulin receptor is often not the only determinant of insulin sensitivity. Although its mechanisms have not been fully clarified yet, insulin resistance mostly results from the activation of intracellular post-receptor signaling pathways. It occurs due to reasons such as post-receptor insulin resistance, signal transmission disorders and GLUT 4 mutations. Thus, although the insulin hormone binds to its receptor, it cannot be effective due to the defect in post-receptor mechanisms. The development of insulin resistance increases with genetic predisposition, obesity, sedentary life, aging. Insulin resistance increases with weight gain and decreases with weight loss. Thus, the importance of fat accumulation in the development of insulin resistance is understood (Chen *et al*. 2010).

2.3.2 Linkage of insulin resistance in hyperthyroidism

Subclinical hyperthyroidism: TSH level is lower than normal (suppressed) even though thyroid hormone levels are normal. Clinical (overt) hyperthyroidism is high T4 and T3 levels and suppressed TSH level (lower than normal value). T3 thyrotoxicosis is characterized by high T3 level and low TSH level while T4 level is normal, more frequently in iodine deficiency regions. Measuring the TSH level is the most sensitive and sensitive test to investigate thyrotoxicosis. In overt hyperthyroidism, fT3 and fT4 are high, and TSH is generally below 0.01 mU/L. In subclinical hyperthyroidism, fT3 and fT4 are normal, TSH is between 0.1 - 0.4 mU/L in mild cases and less than 0.1 mU/L in more severe valars. In the causes of thyrotoxicosis other than hyperthyroidism, ft3 and fT4 are generally high and low TSH (Beylot *et al.* 1980, Rezzonico *et al.* 2011, Peppa *et al.* 2011).

2.3.2.1 The role of the liver

The liver has an important place in the transport, storage, metabolism and excretion of thyroid hormones. T4-carrying proteins, thyroxine-binding globulin (TBG), and prealbumin and albumin are synthesized here. 10-30% of the reversible T4 in the body is in the liver, which is the main place where it is converted to active T3. The liver removes the inactive products of reverse T3 and T4 from the circulation. Studies have shown that

T3 and T4 are rapidly taken up by the liver after intravenous administration; showed that T3'- from the circulation is taken up more quickly than T4 and leaves the liver (Cavallo-Perin *et al.* 1988, Klieverik *et al.* 2009).

2.3.2.2 The role of muscles

Hereditary factors, gender and type 1 diabetes mellitus, excessive thyroid hormone intake can be counted among the risk factors for hyperthyroidism. Hyperthyroidism can also occur due to many reasons such as Graves' disease, inflammation of the thyroid gland or thyroid cancer. Consuming too much iodine can also trigger this disease. To take a brief look at the factors in the formation of this disease:

Graves' Disease: This autoimmune disorder is the most common cause of hyperthyroidism. With Graves' disease, your body attacks healthy thyroid tissue, causing it to overwork. This condition can also lead to graves ophthalmopathy, which affects the tissues and muscles behind the eyes (Shen *et al*. 1988).

2.3.2.3 The role of adipose tissues

A surprising discovery regarding adipose tissue is that it not only functions as a simple depot for triglycerides, but is also an active endocrine organ that secretes many peptides and cytokines. Among the secreted peptides, leptin, adiponectin, resistin can be counted. TNF alpha is known to be secreted as a cytokine. Leptin, resistin and adiponectin are released from white adipose tissue and regulate energy metabolism and insulin sensitivity. Changes in endocrine activity according to the localization of adipose tissue are still under investigation. McGary *et al*. put forward the Lipotoxicity hypothesis to explain the relationship between adipose tissue activity and insulin resistance. They claimed that increased adipose tissue intracellular lipid accumulation impairs certain cellular signaling pathways and functions, thus lipid accumulation plays an important role in the development of insulin resistance (Freake and Oppenheimer 1987).

2.3.3 Linkage of insulin resistance in hypothyroidism

Subclinical (mild) thyroid disease is a common disease especially in middle-aged and elderly patients and is recognized by laboratory parameters. Patients with subclinical hypothyroidism are expected to be asymptomatic due to their normal thyroid hormone levels, but clinical, biochemical and functional findings seen in thyroid hormone deficiency occur in this group. Similarly, subclinical hypothyroidism is more common in individuals with these signs and symptoms. The most obvious complaints in patients; dry skin, weakening of memory, weakening of thought, muscle weakness, weakness, muscle cramps, tingling in the eyes, cold intolerance, constipation and hoarseness of voice. Patients have few clinical signs or symptoms of thyroid dysfunction; sometimes not. Among the obvious signs and symptoms of hypothyroidism, those most associated with subclinical hypothyroidism include neuromuscular dysfunction, deterioration in quality of life, depression, perception and memory disorders, mild systolic and diastolic cardiac dysfunction, increased total LDL cholesterol levels, and increased atherosclerosis. bookmark is located (Harris *et al*. 1993, Rochon *et al*. 2003, Dimitriadis *et al*. 2006, Owecki *et al*. 2006, Handisurya *et al*. 2008).

2.4 Genetic Causes of T2DM and Thyroid Dysfunction

2.4.1 The effect of thyroid hormones on the liver

Iodine, a trace element, forms the main structure of thyroid hormones. Thyroid hormones called triiodothyronine (T3) and tetraiodothyronine (T4) are synthesized as a result of the combination of tyrosine residues called monoiodotyrosine (MIT) and diodotyrosine (DIT) in a large molecule synthesized by thyroglobulin and thyroid follicles. Thyroid stimulating hormone (TSH, thyrotropin) is secreted by the pituitary gland and stimulates important steps during thyroid hormone synthesis. The thyroid gland mainly synthesizes T4 and a small amount of T3, and a significant portion of the active form, circulating T3, results from peripheral deiodination of T4. More than 99% of thyroid hormones circulating in the body are bound to proteins, most notably to thyroid binding globulin (TBG). Only free thyroid hormones enter the cell, the more active form is T3, they control many oxidative events in the whole body through their nuclear receptors (Weinstein *et al*. 1994, Gauthier *et al*. 2010).

2.4.2 Effect of thyroid hormones on skeletal muscle

Thyroid dysfunction can result in musculoskeletal diseases. Thyroid hormones are essential for growth and development, as well as for the optimal functioning of most tissues and organs. Based on this fact, it is not surprising that the musculoskeletal system is affected by thyroid hormone disorders. Muscle involvement is classically associated with hypothyroidism, which can lead to muscle pain, cramping, muscle weakness and hypertrophy of the calf muscles. Patients with hypothyroidism often complain of joint and muscle pain, and may even present with joint effusion involving the knees and small joints. Polymyalgia rheumatica, entrapment neuropathy and tenosynovitis suggesting myopathy in patients presenting with muscle weakness are also diagnoses that should be considered in patients with hypothyroidism (Weitzel *et al.* 2001, Moeller *et al.* 2005, de Lange *et al.* 2007).

The most common musculoskeletal involvement in thyrotoxicosis is decreased bone density. Thyrotoxicosis increases both osteoclastic and osteoblastic activity, but on average, it will be seen that bone resorption, which is the result of osteoclastic activity, is more dominant, especially in trabecular bone. Accordingly, in various studies, excessive hyperthyroidism is associated with osteoporosis. Muscle weakness or loss is another common effect of thyrotoxicosis. Besides these, this Carpal tunnel syndrome, mononeuropathy, and symmetrical peripheral neuropathy have also been described in patients. Irregularities in thyroid hormone may accompany inflammatory diseases (Moreno *et al.* 2011).

The musculoskeletal system is related to the endocrine system both in terms of function and structure. Therefore, it is directly affected by endocrine system disorders. Patients either have a known endocrine disease and apply to us with certain rheumatic complaints or, in the examination performed with rheumatic complaints, these complaints are the finding of an endocrine disease. One of the most important hormones of the endocrine system that affects the musculoskeletal system is thyroid hormone. It is known that thyroid dysfunctions cause rheumatological symptoms and signs such as muscle weakness, fatigue, soft tissue lesions (hypothyroidism, hyperthyroidism), osteopenia (hyperthyroidism). Babies who develop severe hypothyroidism as a result of severe iodine deficiency have cretinism: severe mental retardation with deafness, structural disorders, and tongue enlargement. Iodine supplementation in the first 3 months of pregnancy prevents this picture from occurring; If iodine supplement is left at the end of the 6th month, it will not work. Iodine levels are sufficient in only one fourth of pregnant women in Turkey, mild-moderately low in half, and very low iodine levels in the remaining quarter. Iodine levels are low in 50% of newborns (Boelen 2009, Menconi *et al*. 2010).

2.5 Frequency Of Thyroid Disorders In Diabetes

Although the thyroid is often known as a disease, it is actually an organ located in front of the trachea, under the area of the throat known as the Adam's apple. The thyroid, which resembles the letter U or H and has a butterfly-like shape, is responsible for the production of hormones that regulate many functions in the body. T3 (triiodothyronine) and T4 (thyroxine) hormones as well as calcitonin hormone production, storage and release when necessary, the thyroid is approximately the size of a walnut and its total weight is 15 to 20 g. as much. The middle part of the thyroid, which has a length of four cm and a width of one to two cm, consists of the right and left lobes, is defined as the isthmus in the medical language. The hormones secreted from the thyroid gland mix with the blood circulation and stimulate the relevant system or organ. The regularity of thyroid gland functions, which is very important for body health, affects almost all metabolic processes in the body. In other words, the thyroid gland, which controls the release of hormones that have an effect on many of the activities in the body, is one of the endocrine glands in the body. The functions of the thyroid gland, such as hormone production, storage and release, are controlled by the pituitary gland by stimulating the pituitary gland, another endocrine gland located in the brain, by the TRH hormone secreted by the hypothalamus region in the brain. Before moving on to thyroid gland diseases, "What is thyroid" must answer the question (Canaris *et al.* 2000, Hollowell and Staehling 2002).

The thyroid is located just below the cartilage structure, which is defined as prominentia laryngea in medicine and known as the Adam's apple among the people. This organ, which reveals itself with its butterfly-like structure, moves up and down with swallowing. On the sides of the thyroid gland are arteries defined as the carotid artery. The thyroid gland is activated by the stimulation of the pituitary gland in the brain. The pituitary gland secretes the hormone TSH, which activates the thyroid gland. Also known as thyroid stimulating hormone, TSH reaches the thyroid gland through the circulatory system and triggers the thyroid gland's hormone production. If the thyroid gland secretes a small amount of hormone, the pituitary gland increases the secretion of TSH hormone. Therefore, in thyroid failure disease, which is defined as hypothyroidism, the level of TSH hormone is high, but the level of T3 and T4 hormones secreted by the thyroid gland is low. The TSH hormone measured in the laboratory environment for the diagnosis of thyroid disorders also ensures that the thyroid gland retains iodine. When the thyroid hormone is secreted enough, the level of TSH in the blood decreases(Lindberg *et al.* 1997, Radaideh *et al.* 2004).

In other words, the higher the blood level of T3 and T4 hormones secreted from the thyroid gland, the lower the level of TSH hormone secreted from the pituitary gland in the brain. TSH level falling below the reference range is also called thyroid disease. The condition that occurs due to overactivity of the thyroid gland is defined as hyperthyroidism. The pituitary gland, triggered by the secretion of the appropriate amount of TRH hormone by the hypothalamus region of the brain, controls the release of T3 and T4 hormones of the thyroid gland by releasing TSH hormone. All three endocrine glands must work in harmony in order to maintain metabolic order and stimulate the relevant organs.

2.6 Effects of Thyroid Hormones on Glucose Homeostasis

Thyroid hormones affect glucose metabolism through a variety of mechanisms. It has long been known that hyperthyroidism promotes hyperglycemia. During hyperthyroidism, the half-life of insulin decreases, most likely due to an increased rate of degradation and increased release of biologically inactive insulin precursors (Dimitriadis *et al.*1985, O'Meara *et al.* 1993).

In untreated Graves' disease, increased proinsulin levels in response to a meal were observed in a study by Bech *et al.* Additionally, untreated hyperthyroidism has been associated with a reduced C-peptide:proinsulin ratio, suggesting an underlying defect in proinsulin processing. Another mechanism explaining the relationship between hyperthyroidism and hyperglycemia is the increase in intestinal absorption of glucose mediated by excess thyroid hormones (Levin and Smyth 1963, Matty and Seshadri1965).

In hyperthyroidism, endogenous glucose production is also increased through various mechanisms. Thyroid hormones cause an increase in hepatocyte plasma membrane concentrations of GLUT2, the main glucose transporter in the liver, and consequently increased GLUT-2 levels contribute to increased hepatic glucose output and abnormal glucose metabolism. In addition, increased lipolysis is observed in hyperthyroidism, resulting in an increase in FFA, which stimulates hepatic gluconeogenesis. The increase in FFA secretion can be explained in part by increased catecholamine-induced lipolysis caused by excess thyroid hormones. Also, non-oxidative glucose excretion in hyperthyroidism is enhanced, resulting in excessive lactate production, which enters the Cori cycle and promotes further hepatic gluconeogenesis. The increase in GH, glucagon and catecholamine levels associated with hyperthyroidism contributes more to impaired glucose tolerance (Miki *et al.*1992, Tosi *et al.*1996).

As for hypothyroidism, glucose metabolism is also affected by various mechanisms. A decreased rate of hepatic glucose production is observed in hypothyroidism, explaining the decrease in insulin requirement in hypothyroid diabetic patients. Recurrent hypoglycemic episodes are signs of the development of hypothyroidism in patients with type 1 diabetes, and as Leong et al showed, substitution of thyroid hormones for thyroid hormones reduced fluctuations in blood glucose levels.

2.7 Effects of Diabetes Mellitus on Thyroid Hormones

Thyroid hormones; They increase the metabolism rate of tissues and the rate of oxygen use. Both anabolism and catabolism of proteins are dose-dependently affected by thyroid hormones. Glucose absorption from the intestines, glucose utilization. They increase the rate of gluconeogenesis, mobilize lipids from adipose tissues and increase plasma free fatty acids level and oxidation rate of free fatty acids in cells. The classical effects of these hormones on lipid metabolism are to reduce the amount of cholesterol in the blood plasma. The general function of thyroid hormones is to keep the oxidative metabolism of body tissues at a normal level. Thyroid hormones; The healthy functioning of the thyroid gland is of great importance in terms of human medicine, since they are generally effective on the metabolic activities of the living thing, the development and growth of tissues, the rate of use of nutrients for energy and live weight gain. Under normal conditions, its operation is controlled by the thyrothyroid-releasing hormone (TRH), thyroid stimulating hormone (TSH) and negative feedback mechanism between T4 and T3 in the hypothalamus-pituitary-thyroid axis (Rezzonico *et al.* 2008).

Hypothyroidism is the deficiency of thyroid hormones that occurs in the peripheral tissue as a result of the secretion of small amounts of thyroid hormones, and the picture characterized by an increase in the levels of thyroid hormones as a result of excessive secretion is called hyperthyroidism. In general, enlargement of the thyroid gland is called goiter. Goiter; It can occur as a result of the thyroid gland working more or less, or it can occur as a compensator for the normal function of this gland (Kalmann and Mourits 1999).

2.8 Common Disorders of the Thyroid

There are two main disorders of the thyroid: hypothyroidism, or an underactive thyroid gland, and hyperthyroidism, or an overactive thyroid gland.

2.8.1 Hypothyroidism

Primary hypothyroidism is characterized by increased TSH secretion. Less frequently, central hypothyroidism, which develops as a result of decreased TSH secretion in the pituitary gland, can be seen. Iodine deficiency is the most common cause of hypothyroidism worldwide. It is more common in women than men. It is a clinical condition characterized by a slowdown in metabolism as a result of deficiency of thyroid hormones. In many patients, hypothyroidism is permanent and requires lifelong treatment. The goal of treatment is to achieve and maintain the euthyroid state.

Adult hypothyroidism is a common type of hypothyroidism that manifests itself with clinical symptoms and blood findings. Hypothyroidism and cretinism from infancy vary according to the age at which clinical thyroid hormone deficiency appears in hypothyroidism and the complaint of deficiency. The most important finding is mental retardation. Juvenile hypothyroidism is a type of hypothyroidism that begins in childhood. It lies between infantile and adult hypothyroidism. It may occur in the later stages of life but cannot be diagnosed.

Another type that is difficult to put in place is senile hypothyroidism. Transient hypothyroidism, on the other hand, is a picture of short-term non-severe symptoms and a not very high TSH increase. Subclinical hypothyroidism is characterized by normal serum thyroid hormones (T4) and mildly elevated serum TSH levels.

In iodine-sufficient areas, almost all cases are people under thyroid ablation therapy for thyrotoxicosis or thyroid cancer (radioactive iodine or thyroid surgery), or if these are spontaneously occurring, these are autoimmune thyroiditis (which manifests as atrophic thyroiditis or Hashimoto's disease). Hypothyroidism can occur 20 years or more after radioactive iodine therapy. Years after thyroid surgery or after remissions of Graves' disease induced by carbimazole (this is not seen in multinodular goiters), hypothyroidism can be seen as a result of the autoimmune reaction turning into a spontaneously destructive picture or as a result of the disappearance of the thyroid stimulating antibodies. Although anti-TPO antibodies are seen in more than 90% of chronic autoimmune thyroiditis, negative results are also common in routine clinical observations.

The last category leading to primary hypothyroidism is congenital defects that impair the functions of the thyroid gland. TSH receptor mutations, paired box containing gene mutations (PAX 8), thyroid transcription factor 2 (TTF2) gene mutations were found to cause hypothyroidism together with thyroid hypoplasia, and primary hypoadrenalism was also found in one case. Sodium/iodine transporter (simporter) or thyroid peroxidase enzyme mutations together with hypothyroidism and goiter were detected, and the perchlorate excretion test was positive in the case with thyroid peroxidase enzyme mutations. Many thyroglobulin synthesis defects with very low T4 levels have been detected with various degrees of hypothyroidism and goiter.

Most of the clinical signs and symptoms in hypothyroidism develop due to the change in the rate of physiological events. The most common symptoms are; weakness, fatigue, tendency to sleep, mental dysfunction, depression, chills easily, changes in voice tone, moisture loss in the skin, loss of appetite, constipation and menstrual irregularity. In addition to all these clinical findings, metabolic conditions that can be considered as complications are hypercholesterolemia, hyperprolactinemia, anemia, hyponatremia, increased homocysteine, increased creatinine kinase and lactate dehydrogenase.

2.8.2 Hyperthyroidism

Hyperthyroidism is a clinically common syndrome with dramatic consequences. It is a condition created by physiological, biological and clinical findings, which occurs when the surrounding tissues are under the influence of high levels of hormones as a result of excessive elevation of thyroid hormones in the blood, resulting in hypermetabolism. There is a general acceleration in metabolism. The term 'thyrotoxicosis' is sometimes used to describe this syndrome. Symptoms include nervousness, irritability, excessive sweating, increased blood pressure and respiration, tachycardia, dyspnea, diarrhea, goiter, exophthalmos, and skin changes.

Graves' disease is a very common autoimmune disease. Thyrotoxicosis presents with diffuse goiter, infiltrative ophthalmopathy and thyroid acropathy. Antithyroid drugs, lithium carbonate, radioactive iodine and dexsometasone are used in the treatment of hyperthyroidism. thyrotoxicosis; It is a picture characterized by hypermetabolism and hyperactivity syndrome, in which serum concentrations of T4, T3 or both are increased. Diseases that cause hyperthyroidism may originate from the thyroid gland, as well as from pituitary or non-pituitary causes.

Hyperthyroidism; It is divided into 3 groups as primary, secondary and subclinical hyperthyroidism.

Primary hyperthyroidism: It may develop due to Graves' disease, TMNG, TA and functional thyroid carcinoma metastases.

Secondary hyperthyroidism: It is less common. TSH-secreting pituitary adenoma can be shaped due to thyroid hormone resistance syndrome and gestational thyrotoxicosis.

Subclinical hyperthyroidism: It is a condition characterized by low TSH levels, but having serum T3 and T4 levels within normal limits. The causes are the same as the causes of hyperthyroidism. The most common cause is thyroid hormone taken from outside. The frequency of endogenous subclinical hyperthyroidism is only 0.6 – 1.1%. Causes of endogenous subclinical hyperthyroidism include insufficiently treated hyperthyroidism, early Graves' hyperthyroidism, iodine-induced hyperthyroidism, solitary autonomic adenoma, and thyroiditis. Symptoms in subclinical hyperthyroidism cases It may not be obvious or it may be moderate.

2.9 Effect on Diabetes Control

Because normal thyroid function is essential for regulating energy metabolism, abnormal thyroid function can have major effects on blood glucose control in diabetes. Both hyperthyroidism and hypothyroidism can affect the course of diabetes, but their effects are somewhat different.

2.9.1 Hyperthyroidism

The clinical syndrome that occurs when tissues are exposed to high levels of circulating thyroid hormones is called thyrotoxicosis and is often due to increased thyroid function, namely hyperthyroidism. Almost the most common cause of thyrotoxicosis is Grave's disease; This disease can be seen in all ages and genders and is an autoimmune disease of unknown cause. Regardless of the source of thyrotoxicosis, it is the general term expressing thyroid hormone excess. Hyperthyroidism refers to the excess of thyroid hormone resulting from increased thyroid hormone production from the thyroid gland.

Hyperthyroidism can also be defined as a hypermetabolic state accompanied by increased oxygen use and changes in antioxidative factors as a result of the formation of reactive oxygen products. While this condition is associated with heart diseases, complications are acceptable. Grave's Disease, excessive iodine intake or the use of certain drugs can be counted as the causes of the disease.

2.10 Treatment of Thyroid Disease

Almost all thyroid diseases can be treated. Hypothyroidism and hyperthyroidism usually require long-term or lifelong treatment, depending on the type.

2.10.1 Hypothyroidism

The treatment of hypothyroidism is most often done by giving thyroid hormone support to the patient. For this purpose, a drug called levothyroxine is used. For dose adjustment, occasional blood tests should be performed initially. This setup may take some time. In women who are considering having a child; It is important for the health of themselves and their babies to treat hypothyroidism appropriately before becoming pregnant. For this reason, pregnant women and those who have a pregnancy plan should definitely report this to the doctor if they are hypothyroid patients. In cases of hypothyroidism caused by iodine deficiency, iodine-rich foods are added to the diet to ensure adequate iodine intake.

2.10.2 Hyperthyroidism

There are 3 methods in the treatment of hyperthyroidism:

1. Drug therapy.
2. Atom (Radioactive iodine) therapy, Surgery.

Drug Treatment: All patients with hyperthyroidism are first started on drug therapy in order to normalize the high levels of thyroid hormones in the blood. Your doctor adjusts the dose of the drug according to the severity of the disease. After 6 - 8 weeks of starting the drug treatment, you will be called for control again and the dosage of the drug will be adjusted according to the state of your hormones. In this way, check-ups are made every 1.5 - 2 months, and drug treatment is continued for at least 9 months - 1 year, and the drug can be discontinued according to your doctor's decision. If the drug is stopped without the doctor's knowledge, the disease will flare up again. Thus, the treatment done until that time will be in vain. Therefore, drug therapy should not be stopped without consulting your doctor. If you have a fever and sore throat during medication, you should consult your doctor immediately. This may be due to the very decrease in white cells (leukocytes) in the blood. If this rare condition occurs, the drugs are discontinued and surgical treatment or atomic therapy is recommended. During treatment, your liver may be affected and there may be mild elevations in liver-related blood levels. However, this may also be due to the effect of hyperthyroidism. For this reason, the enzyme levels called SGOT (AST) and SGPT (ALT) should be monitored frequently and if the enzyme levels increase gradually with the treatment, the drugs should be discontinued and the patient should be offered surgery or switched to atom therapy. If the patient has a 'hot nodule' after the drug is stopped, surgery or atomic treatment is performed after the hormone levels are brought back to normal with drugs. One thing is that they don't eat iodized salt.

Patients with hyperthyroidism should eat non-iodized salt. Since the disease is difficult to recover and eye disease occurs in smokers, the patient should quit smoking.

2.11 Hypothyroidism in Women

Hypothyroidism is the second most common type of endocrine disorder affecting women of reproductive age, but it can affect women throughout life. The thyroid maintains metabolism and vital body functions. It is located in the anterior neck just below the larynx and consists of two lobes connecting the trachea. Hypothyroidism occurs when the thyroid gland does not produce enough thyroid hormone.

The risk of developing hypothyroidism in women increases with age and during pregnancy, postpartum period and menopause (Garber *et al.* 2012). Iodine deficiency is the most common cause of hypothyroidism worldwide (Vanderpump 2011). Hashimoto's thyroiditis, the most common cause of hypothyroidism in the United States, results from damage to the thyroid gland caused by chronic inflammation initiated and maintained by one's own immune system (Zaletel and Gaberšček 2011).

This autoimmune reaction causes insufficient production of thyroid hormone and is 5 to 10 times more common in women than men (Garber *et al.* 2012). Medical treatments can also cause hypothyroidism. Treatment of certain thyroid conditions, such as thyroid cancer, goiter, and Graves' disease, may require surgical removal of part of the thyroid gland or thyroidectomy. If enough glands are removed, the thyroid cannot produce enough thyroid hormone, causing hypothyroidism. Additionally, some other thyroid conditions and cancers may require treatment with radioactive iodine or external radiation, which can damage the thyroid and often results in overt hypothyroidism. Some medications can cause hypothyroidism by affecting the thyroid gland's hormone production or release. Drugs such as amiodarone, interferon and lithium have been identified as a cause of hypothyroidism (Barbesino 2010).

Pathophysiology: Hypothyroidism is a relatively common disease. The incidence of hypothyroidism increases with aging and is 5 - 10 times more common in women than in men. Hypothyroidism is especially common in iodine-deficient areas. In addition, the incidence of hypothyroidism increases in patients with positive thyroid peroxidase autoantibodies (TPO) and those with thyroid stimulating hormone (TSH) at the upper limits of normal. The incidence of overt hypothyroidism has been reported between 0.1-2%. Subclinical hypothyroidism is much more common. It can be seen between 4-10% in adults and around 15% especially in elderly women. In a study conducted in the United States, serum TSH, T4, anti-TPO and anti-thyroglobulin (anti TG) antibodies were measured in 13,344 individuals who were not known to have thyroid disease, 1.3% had hyperthyroidism (0.5% overt and 0.7% subclinical hyperthyroidism) and 11% had anti-TPO positivity.

Hypothyroidism can be temporary, permanent, central or primary. Central hypothyroidism develops as a result of hypothalamo-pituitary diseases as a result of decreased TSH secretion or biological activity. Primary hypothyroidism, on the other hand, occurs as a result of decreased synthesis and secretion of thyroid hormones as a result of a disease in the thyroid gland.

Diagnosis: Diagnosis is made as a result of clinical and laboratory evaluation. Generally, the diagnosis is easily made by measuring thyroid hormones in patients with appropriate clinics. However, in some rare cases, the diagnosis may be more difficult or may require further investigations. Many conditions (such as estrogen use, nephrotic syndrome) that affect the level of thyroxine-binding globulin can also affect serum total T4 (TT4) and total T3 (TT3) levels. For this reason, fT4 and fT3 measurement is preferred. As a screening test, TSH is measured first, if TSH is high, fT4 and, if necessary, fT3 are measured. In primary hypothyroidism, plasma TSH is high and fT4 is low. fT3 usually begins to decline in the advanced stage of hypothyroidism. The condition in which fT3 and fT4 are normal but TSH is increased is called subclinical hypothyroidism. In central hypothyroidism, with low fT4, TSH may be low or normal or, more rarely, slightly elevated (immunoreactive TSH) (Indra *et al.* 2004).

If the diagnosis is primary hypothyroidism (overt or subclinical), anti-TPO antibody and anti-TG antibody are measured to reveal the etiology. In autoimmune hypothyroidism, thyroid antibodies (anti TPO and anti TG) are generally positive and titer is high. The history of thyroidectomy or RAI treatment is important in terms of revealing the etiology (Garber *et al.* 2012). It is also important to question the drugs that can lead to hypothyroidism. If thyroid function tests support central hypothyroidism, euthyroid sick syndrome should be considered in the differential diagnosis. If there is no euthyroid sick syndrome or a definite distinction cannot be made, pituitary imaging (preferably pituitary MRI) is performed in terms of central hypothyroidism. Since any pathology causing central hypothyroidism will usually affect other pituitary hormones, other pituitary hormones are also measured (Ross *et al.* 2019).

Other tests are available in addition to the thyroid function test. A specialist may evaluate anti-thyroid microsomal antibodies, such as anti-thyroid peroxidase, to further determine the cause of hypothyroidism. The presence of these antibodies indicates that thyroid damage has occurred, which can lead to hypothyroidism. This test may be indicated in a woman with a goiter or a symptomatic woman with a normal TSH level.

Symptoms: The symptoms of hypothyroidism are similar to the symptoms of many different diseases. Symptoms of hypothyroidism; weakness, fatigue, difficulty in concentration, constipation, cold quickly and intolerance to cold (Garber *et al*. 2012). Dry skin, coarsening of the skin, and changes in color that turn orange, which are sometimes thought to be caused by dermatological diseases, may also develop due to under-functioning of the thyroid gland. The symptoms and complaints that can be seen in hypothyroidism vary depending on the severity of the deficiency in hormones. Symptoms are vague at first and gradually become apparent over several years. Initially, nonspecific symptoms such as fatigue and weight gain are encountered. The following signs and symptoms can be observed when the slowdown in the metabolic rate becomes evident due to the deficiency of thyroid hormones (Garber et al. 2012):

- ✓ Weakness.
- ✓ Constipation.
- ✓ Dry skin.
- ✓ Sensitivity to cold.
- ✓ Increase in weight.
- ✓ Swelling of the face, hands and feet
- ✓ Hoarseness.
- ✓ Weakness in muscles.
- ✓ Increase in blood cholesterol level.
- ✓ Pain, tenderness and stiffness in the muscles.
- ✓ Pain, stiffness, or swelling in the joints.
- ✓ Irregular menstrual periods.
- ✓ Painful menstruation.
- ✓ Hair thinning
- ✓ Thin brittle hair and nails
- ✓ Slow heart rate.
- ✓ Depressed mood.
- ✓ Memory impairment.
- ✓ Enlargement of the thyroid gland (Goiter).
- ✓ Balance and coordination problems.
- ✓ Loss of libido.
- ✓ Anemia.
- ✓ Decreased sweating.
- ✓ Insomnia.
- ✓ Sparseness of the eyebrows.
    - hearing problems.

3. MATERIALS AND METHODS

Middle-aged women (45-65 years old) will be selected to participate in this study, they will consist of people with a previous diagnosis of hypothyroidism and no other chronic diseases.

The study will be carried out over a period of 6 months. The work plan is as follows.

a) To investigate the incidence of T1DM and T2DM in patients with pre-existing hypothyroidism.

b) To determine the incidence of hypothyroidism with pre-existing T1DM and T2DM.

Enrolled diabetic patients will be receiving insulin and/or oral hypoglycemic agents, and hypothyroid patients will be receiving levothyroxine (25/50/75/88/100/125 mcg). An appropriate data collection form will be designed to collect, document and analyze the data. All relevant and necessary data regarding blood glucose and thyroid profiles will be collected from the laboratory reports of the patients. The total study population will be 100 patients, of whom 50 will have preexisting T1DM and T2DM and 50 will have preexisting hypothyroidism. At the end of the study, hypothyroidism, lower T3 and T4 levels and higher TSH levels than laboratory reference values will be evaluated according to the thyroid profile.

3.1 Statistical Analysis

Data will be analyzed using GraphPad Prism software version 6.0. Quantitative data will be expressed using mean and standard deviation, while qualitative data will be expressed as frequency and percentage. Quantitative data will be analyzed using the non-parametric Kruskal-Wallis test to compare the two groups. P value of 0.05 or less will be assumed to be significant.

3.2 Patients' Choice

The experimental study is carried out with patients divided into two groups. The study was carried out with a total of 100 patients, 50 in each study group. Common criteria for each patient are:

- Patients being women.
- The age range of the patients is between 45 – 65 years old.
- The patients do not have any disease that will affect the working conditions and results.
- Patients should not use any drugs that will affect their working conditions and results. chemotherapy, radiotherapy, etc. not in a treatment process.
- Patients' mental health and their willingness to participate in the study.

3.2.1 First group

In the first group, the incidence of Type 1 and Type 2 Diabetes was investigated in female patients previously diagnosed with hypothyroidism.

In addition to the above-mentioned common criteria, the following criteria were taken into account in the selection of patients in the first group:

- Patients diagnosed with hypothyroidism.

- Initiation of treatment for hypothyroidism with levothyroxine. In the treatment with levothyroxine, the dose amount can vary between 25 – 125 mcg.

3.2.2 Second group

In the second group, the incidence of hypothyroidism was investigated in female patients previously diagnosed with Type 1 or Type 2 Diabetes.

In the selection of the patients forming the second group, the following criteria were taken into consideration in addition to the common criteria mentioned above:

- Patients diagnosed with Type 1 or Type 2 diabetes.
- Initiation of therapy with insulin and/or oral hypoglycemic agents.

3.3 Collection of Samples

In order to control the incidence of hypothyroidism in Type 1 and Type 2 Diabetes and diabetes in hypothyroidism, 20 mL blood samples were taken from the patients in two tubes, 10 mL in each tube. Samples were taken in 10 ml gel tubes with yellow caps.

Samples were taken from all patients between 09:00 and 09:30 on the same day, as agreed before, and transferred to the biochemistry laboratory without waiting.
It was verified that each participant met the 12-hour fasting condition.
In the experimental study, the precautions taken for the COVID-19 epidemic disease were complied with.

Analyzes were performed automatically, spectrophotometrically, using the Cobas C311,E411 (Roche) Autoanalyzer. Details for each parameter controlled from blood samples are given below:

3.3.1 Serum glucose

As a marker of Type 1 and Type 2 Diabetes, fasting glucose values of both experimental groups were measured. Information about the fasting glucose test and serum glucose measurement are illustrated in Table 3.1.

Serum glucose values of a total of 100 female patients in two study groups consisting of 50 people between the ages of 45 and 65 were measured, and the results obtained for group 1 and group 2 are given in the results section.

Table 3.1 Serum glucose measurement information

Test	Serum glucose
Sample collection time	09:00
Laboratory departure time	09:30
Results time	10:15
Sample type	Serum
Sample container	Yellow capped gel tube
Sample volume	10 mL
Sample analysis method	Cobse311
Reference range (mg/dL)	74 – 106
Sample purpose of use	Type 2 diabetes detection
Number of samples	100
Number of result approvals	100 / 100

3.3.2 Thyroid stimulating hormone (TSH)

TSH values of a total of 100 female patients were measured in two study groups consisting of 50 people between the ages of 45 and 65, and the results obtained for group 1 and group 2 are given in the results section, TSH measurement information are illustrated in Table 3.2.

Table 3.2 TSH measurement information

TEST	TSH (Thyroid Stimulating Hormone/ Thyrotropin)
Sample collection time	09:00
Laboratory departure time	09:30
Results time	10:15
Sample type	Serum
Sample container	Yellow capped gel tube
Sample volume	10 mL
Sample analysis method	Cobse 411
Reference range (µU/mL)	0.55 – 4.78
Sample purpose of use	Thyroid functions analysis
Number of samples	100
Number of result approvals	100 / 100

3.3.3 Free T3 hormone

FT3 values of a total of 100 female patients were measured in two study groups consisting of 50 people between the ages of 45 and 65, and the results obtained for group 1 and group 2 are given in the results section, free T3 hormone measurement information are illustrated in Table 3.3.

Table 3.3 Free T3 hormone measurement information

Test	**(Free T3 / Triiodothyronine)**
Sample collection time	09:00
Laboratory departure time	09:30
Results time	10:15
Sample type	Serum
Sample container	Yellow capped gel tube
Sample volume	10 mL
Sample analysis method	Cobse411
Reference range (pg/mL)	2.3 – 4.2
Sample purpose of use	Thyroid functions analysis
Number of samples	100
Number of result approvals	100 / 100

3.3.4 Free T4 hormone

FT4 values of a total of 100 female patients were measured in two study groups consisting of 50 people between the ages of 45 and 65, and the results obtained for group 1 and group 2 are given in the results section, Free T4 hormone measurement information are illustrated in Table 3.4.

Table 3.4 Free T4 hormone measurement information

TEST	**(Free T4 / Triiodothyronine)**
Sample collection time	09:00
Laboratory departure time	09:30
Results time	10:15
Sample type	Serum
Sample container	Yellow capped gel tube
Sample volume	10 mL
Sample analysis method	Cobse411
Reference range (ng/dL)	0.89 – 1.76
Sample purpose of use	Thyroid functions analysis
Number of samples	100
Number of result approvals	100 / 100

3.3.5 HbA1c

The HbA1c values of a total of 100 female patients were measured in two study groups, each consisting of 50 people between the ages of 45 and 65, and the results obtained for group 1 and group 2 are given in the results section, HbA1c measurement information are illustrated in Table 3.5.

Table 3.5 HbA1c measurement information

Test	**HbA1c**
Sample collection time	09:00
Laboratory departure time	09:30
Results time	12:30
Sample type	Blood
Sample container	Purple cap gel tube EDTA
Sample volume	3 mL
Sample analysis method	Cobs C311
Reference range (%)	4.2 - 6.5
Sample purpose of use	HbA1c Analysis
Number of samples	100
Number of result approvals	100 / 100

3.3.6 Insulin

Insulin values of a total of 100 female patients were measured in two study groups consisting of 50 people between the ages of 45 and 65, and the results obtained for group 1 and group 2 are given in the results section. Insulin measurement information are illustrated in Table 3.6.

Table 3.6 Insulin measurement information

Test	**Insulin**
Sample collection time	09:00
Laboratory departure time	09:30
Results time	10:00
Sample type	Serum
Sample container	Yellow capped gel tube
Sample volume	5 mL
Sample analysis method	Cobas C411
Reference range (μU/mL)	2.6-24.9
Sample purpose of use	Insulin analysis
Number of samples	100
Number of result approvals	100 / 100

4. RESULTS

4.1 First Group

The patients in the first group are female patients between the ages of 45 and 65 who have been diagnosed with hypothyroidism and continue their treatment with Levothyroxine. The mean age of these patients was calculated as 53.92 ± 7.01. It is illustrated in Table 4.1.

None of the patients in the first group reported the use of drugs, alcohol, cigarettes and other tobacco products.

Table 4.1 Age statistics of female patients in the first group

Patient No	Gender	Age
1	Woman	45
2	Woman	62
3	Woman	57
4	Woman	49
5	Woman	48
6	Woman	64
7	Woman	51
8	Woman	57
9	Woman	53
10	Woman	50
11	Woman	45
12	Woman	46
13	Woman	45
14	Woman	45
15	Woman	52
16	Woman	65
17	Woman	61
18	Woman	49
19	Woman	52
20	Woman	61
21	Woman	54
22	Woman	56
23	Woman	63
24	Woman	46

Table 4.1 Age statistics of female patients in the first group (Continued)

25	Woman	61
26	Woman	64
27	Woman	58
28	Woman	46
29	Woman	51
30	Woman	48
31	Woman	47
32	Woman	45
33	Woman	62
34	Woman	54
35	Woman	51
36	Woman	64
37	Woman	65
38	Woman	65
39	Woman	46
40	Woman	61
41	Woman	48
42	Woman	54
43	Woman	52
44	Woman	53
45	Woman	61
46	Woman	64
47	Woman	42
48	Woman	48
49	Woman	50
50	Woman	60
Average	53.92	
S. Deviation	7.015551	

The mean FT3 hormone of female patients diagnosed with hypothyroidism in the first group was calculated as 1.79 ± 0.44, it is shown in Table 4.1. This mean value is lower than the lower limit of 2.3 pg/mL of the reference values of 2.3 – 4.2 pg/mL. It is evaluated that the levothyroxine treatments of the patients, the positive lifestyle and nutritional changes they make within the scope of disease follow-up and disease control have an impact on this value.

Table 4.2 FT3 value statistics of female patients in the first group

Patient No	**Gender**	**FREE T3 (pg/mL)**
1	Woman	1.75
2	Woman	1.82
3	Woman	1.5
4	Woman	1.74
5	Woman	1.92
6	Woman	2.11
7	Woman	2.01
8	Woman	2.00
9	Woman	1.80
10	Woman	1.87
11	Woman	1.94
12	Woman	1.14
13	Woman	1.11
14	Woman	1.14
15	Woman	1.87
16	Woman	2.35
17	Woman	1.66
18	Woman	1.85
19	Woman	1.19
20	Woman	2.05
21	Woman	1.75
22	Woman	1.42
23	Woman	0.99
24	Woman	1.17
25	Woman	1.94
26	Woman	2.15
27	Woman	2.22
28	Woman	2.09
29	Woman	1.82
30	Woman	2.04
31	Woman	2.10
32	Woman	1.47
33	Woman	1.98
34	Woman	1.87
35	Woman	1.63
36	Woman	1.77
37	Woman	1.81
38	Woman	1.43
39	Woman	1.76
40	Woman	1.25
41	Woman	1.44
42	Woman	2.52

Table 4.2 FT3 value statistics of female patients in the first group (Continued)

43	Woman	1.75
44	Woman	1.43
45	Woman	1.89
46	Woman	2.21
47	Woman	3.75
48	Woman	1.84
49	Woman	1.72
50	Woman	1.80
Average		1.79660
S. Deviation		0.441891

The mean FT4 hormone of female patients diagnosed with hypothyroidism in the first group was calculated as 0.75 ± 0.19, it is illustrated in Table 4.3. This mean value is lower than the lower limit 0.89 ng/dL of the reference values of 0.89 – 1.46 ng/dL. It is evaluated that the levothyroxine treatments of the patients, the positive lifestyle and nutritional changes they make within the scope of disease follow-up and disease control have an impact on this value.

Table 4.3 FT4 value statistics of female patients in the first group

Patient No	Gender	FT4 (ng/dL)
1	Woman	0.88
2	Woman	0.76
3	Woman	0.52
4	Woman	0.76
5	Woman	0.71
6	Woman	0.82
7	Woman	0.54
8	Woman	0.87
9	Woman	0.85
10	Woman	0.75
11	Woman	0.82
12	Woman	0.72
13	Woman	0.64
14	Woman	0.56
15	Woman	0.82
16	Woman	0.89
17	Woman	0.71
18	Woman	0.62
19	Woman	0.71
20	Woman	0.91
21	Woman	0.75
22	Woman	0.82
23	Woman	0.64
24	Woman	0.77
25	Woman	0.82
26	Woman	0.81
27	Woman	1.12
28	Woman	0.97
29	Woman	0.66
30	Woman	0.94
31	Woman	1.25
32	Woman	0.61
33	Woman	0.74
34	Woman	056
35	Woman	0.91
36	Woman	0.72
37	Woman	0.64
38	Woman	0.43
39	Woman	0.71
40	Woman	0.32
41	Woman	0.56
42	Woman	1.05
43	Woman	0.77
44	Woman	0.85
45	Woman	0.56
46	Woman	0.77
47	Woman	1.43
48	Woman	0.45
49	Woman	0.85
50	Woman	0.56
Average		0.758000
S. Deviation		0.198268

The mean TSH hormone of female patients diagnosed with hypothyroidism in the first group was calculated as 5.64 ± 0.76, it is illustrated in Table 4.4. This mean value is higher than the upper limit of the reference values of 0.55 – 4.78 µU / mL , 4.78 µg / mL. It is evaluated that the levothyroxine treatments of the patients, the positive lifestyle and nutritional changes they make within the scope of disease follow-up and disease control have an impact on this value.

Table 4.4 TSH value statistics of female patients in the first group

Patient No	**Gender**	**TSH (µU/ML)**
1	Woman	5.15
2	Woman	6.42
3	Woman	6.74
4	Woman	7.15
5	Woman	4.92
6	Woman	5.51
7	Woman	6.23
8	Woman	7.45
9	Woman	6.75
10	Woman	6.42
11	Woman	5.14
12	Woman	5.82
13	Woman	4.77
14	Woman	4.95
15	Woman	5.46
16	Woman	5.67
17	Woman	5.44
18	Woman	5.21
19	Woman	6.14
20	Woman	6.88
21	Woman	5.12
22	Woman	5.20
23	Woman	5.55
24	Woman	6.17
25	Woman	4.99
26	Woman	5.14
27	Woman	5.47
28	Woman	6.21
29	Woman	5.88
30	Woman	5.10
31	Woman	5.00

Table 4.4 TSH value statistics of female patients in the first group (Continued)

32	Woman	4.97
33	Woman	5.25
34	Woman	6.99
35	Woman	7.12
36	Woman	4.91
37	Woman	3.42
38	Woman	5.64
39	Woman	4.95
40	Woman	5.41
41	Woman	6.12
42	Woman	5.20
43	Woman	5.71
44	Woman	5.74
45	Woman	5.71
46	Woman	6.11
47	Woman	4.92
48	Woman	5.45
49	Woman	5.22
50	Woman	5.19
Average		5.64160
S. Deviation		0.76452

The mean Serum Glucose (Fasting Blood Sugar) of female patients diagnosed with hypothyroidism in the first group was calculated as 133.18 ± 57.62, it is illustrated in Table 4.5. This mean value is higher than the upper limit of the reference values of 74 – 106 mg/dL, 106 mg/dL. Although this average value does not mean that all hypothyroid patients are diabetic, it indicates that the group is generally at risk of developing Type 2 Diabetes. Although rare, there are patients with normal blood sugar levels in the group, but it is seen at values far above the normal reference range as illustrated in Table 4.5. This situation can also be understood from the standard deviation value.

Table 4.5 Serum glucose value statistics of female patients in the first group

Patient No	**Gender**	**Serum glucose (**mg/dL**)**
1	Woman	85
2	Woman	82
3	Woman	94
4	Woman	102
5	Woman	214
6	Woman	109
7	Woman	115
8	Woman	124
9	Woman	105
10	Woman	94
11	Woman	152
12	Woman	265
13	Woman	112
14	Woman	94
15	Woman	128
16	Woman	117
17	Woman	110
18	Woman	99
19	Woman	85
20	Woman	210
21	Woman	99
22	Woman	104
23	Woman	147
24	Woman	111
25	Woman	297
26	Woman	312
27	Woman	133
28	Woman	194
29	Woman	145
30	Woman	103
31	Woman	101
32	Woman	206
33	Woman	290
34	Woman	185
35	Woman	97
36	Woman	88
37	Woman	117
38	Woman	145
39	Woman	93
40	Woman	106
41	Woman	106

Table 4.5 Serum glucose value statistics of female patients in the first group (Continued)

42	Woman	105
43	Woman	98
44	Woman	115
45	Woman	163
46	Woman	110
47	Woman	105
48	Woman	91
49	Woman	97
50	Woman	100
Average		133.18000
S. Deviation		57.62960

The blood averages of female patients with hypothyroidism in the first group were (7.23 ± 0.75) as illustrated in Table 4.6. The normal value of the test is 4.2-6.5%. While this mean value does not mean that all thyroid patients have diabetes, it does indicate that the group is at risk for developing diabetes in general. Although rare, there are patients with normal blood glucose levels in the group, but it is observed at values far above the normal reference range.

Table 4.6 HbA1c statistics of female patients in the first group

Patient No	**Gender**	**HBA1C (%)**
1	Woman	6.6
2	Woman	6.7
3	Woman	7.0
4	Woman	6.4
5	Woman	6.9
6	Woman	7.5
7	Woman	6.5
8	Woman	7.1
9	Woman	8.0
10	Woman	6.3
11	Woman	6.6
12	Woman	6.4
13	Woman	7.3
14	Woman	8.1

Table 4.6 HbA1c statistics of female patients in the first group (Continued)

15	Woman	6.9
16	Woman	6.2
17	Woman	6.8
18	Woman	7.2
19	Woman	9.0
20	Woman	7.9
21	Woman	6.6
22	Woman	6.7
23	Woman	6.4
24	Woman	8.2
25	Woman	7.3
26	Woman	6.5
27	Woman	6.9
28	Woman	9.5
29	Woman	6.7
30	Woman	7.8
31	Woman	7.7
32	Woman	7.0
33	Woman	6.9
34	Woman	8.7
35	Woman	6.9
36	Woman	7.8
37	Woman	7.0
38	Woman	6.1
39	Woman	6.9
40	Woman	7.4
41	Woman	8.1
42	Woman	8.6
43	Woman	7.8
44	Woman	7.2
45	Woman	6.8
46	Woman	7.1
47	Woman	8.0
48	Woman	6.7
49	Woman	7.0
50	Woman	7.8
Average		7.23
S. Deviation		0.75

The mean insulin value is illustrated in Table 4.7 for female patients with hypothyroidism in the first group was calculated as 26.142 ± 1.31. The normal insulin value was 2.6 - 24.9. It turned out that there was an increase in insulin.

Table 4.7 Insulin value statistics of female patients in the first group

Patient No	Gender	Insulin (µU/ML)
1	Woman	27
2	Woman	28.2
3	Woman	25.4
4	Woman	24.8
5	Woman	25.1
6	Woman	24.7
7	Woman	27.1
8	Woman	25.9
9	Woman	25.1
10	Woman	25.0
11	Woman	25.9
12	Woman	26
13	Woman	25.1
14	Woman	26.2
15	Woman	25
16	Woman	24.5
17	Woman	24.9
18	Woman	25.0
19	Woman	25.9
20	Woman	27.9
21	Woman	26.2
22	Woman	26.7
23	Woman	24.8
24	Woman	24.8
25	Woman	26.1
26	Woman	27.8
27	Woman	24.2
28	Woman	26.3
29	Woman	27.1
30	Woman	25.9
31	Woman	26.5
32	Woman	28.0
33	Woman	27.5
34	Woman	26.3
35	Woman	25.4

Table 4.7 Insulin value statistics of female patients in the first group (Continued)

36	Woman	27.9
37	Woman	26.0
38	Woman	25.6
39	Woman	24.8
40	Woman	27.0
41	Woman	28.9
42	Woman	29.0
43	Woman	26.5
44	Woman	25.9
45	Woman	25.0
46	Woman	24.6
47	Woman	27.8
48	Woman	25.6
49	Woman	24.7
50	Woman	29.5
Average		26.142
S. Deviation		1.31

4.2 Second Group

The patients in the second group are female patients between the ages of 45 and 65 who have been diagnosed with Type 1 or Type 2 Diabetes and continue their treatment with insulin hormone replacement or oral hypoglycemic agents. The mean age of these patients was calculated as 55.30 ± 6.91 years, it is illustrated in Table 4.8.

None of the patients in the second group reported the use of drugs, alcohol, cigarettes and other tobacco products.

The 50 patients in the second group were coded in the range of 51-100 to avoid confusion with the first group.

Table 4.8 Age statistics of female patients in the second group

Patient No	Gender	Age
51	Woman	64
52	Woman	61
53	Woman	62
54	Woman	62
55	Woman	65
56	Woman	45
57	Woman	47
58	Woman	51
59	Woman	46
60	Woman	57
61	Woman	53
62	Woman	59
63	Woman	55
64	Woman	61
65	Woman	64
66	Woman	52
67	Woman	61
68	Woman	58
69	Woman	59
70	Woman	49
71	Woman	45
72	Woman	55
73	Woman	50
74	Woman	45
75	Woman	45
76	Woman	60
77	Woman	61
78	Woman	65
79	Woman	48
80	Woman	56
81	Woman	65
82	Woman	65
83	Woman	57
84	Woman	50
85	Woman	54
86	Woman	57
87	Woman	61
88	Woman	60
89	Woman	50
90	Woman	62
91	Woman	65

Table 4.8 Age statistics of female patients in the second group (Continued)

92	Woman	64
93	Woman	60
94	Woman	50
95	Woman	45
96	Woman	46
97	Woman	47
98	Woman	45
99	Woman	50
100	Woman	51
Average		55.30000
S. Deviation		6.911245

The mean FT3 hormone of female patients diagnosed with hypothyroidism in the second group was calculated as 2.11 ± 0.64, it is illustrated in Table 4.9. This mean value is lower than the lower limit of 2.3 pg/mL of the reference values of 2.3 – 4.2 pg/mL. This result shows that FT3 hormone levels of diabetic patients are slightly below the lower reference value and reveals that FT3 deficiency, which is one of the markers of hypothyroidism, can be seen in Diabetes patients. Although FT3 values are within the reference value range in some of the 50 female patients with diabetes, whom you have been treated individually, the group mean is below the reference value.

Table 4.9 Free T3 value statistics of female patients in the second group

Patient No	Gender	T3 (pg/mL)
51	Woman	2.14
52	Woman	1.75
53	Woman	2.43
54	Woman	2.25
55	Woman	1.76
56	Woman	2.10
57	Woman	2.00
58	Woman	1.78
59	Woman	1.45
60	Woman	1.33
61	Woman	3.25
62	Woman	1.55
63	Woman	1.99
64	Woman	1.57
65	Woman	3.56
66	Woman	2.22
67	Woman	1.94
68	Woman	1.85
69	Woman	1.45
70	Woman	1.56
71	Woman	1.77
72	Woman	2.04
73	Woman	1.95
74	Woman	1.56
75	Woman	3.15
76	Woman	2.56
77	Woman	2.75
78	Woman	1.41
79	Woman	2.01
80	Woman	1.97
81	Woman	1.12
82	Woman	1.99
83	Woman	2.43
84	Woman	4.12
85	Woman	3.22
86	Woman	2.01
87	Woman	1.85
88	Woman	1.99
89	Woman	2.01
90	Woman	1.87
91	Woman	3.12
92	Woman	3.93

Table 4.9 Free T3 value statistics of female patients in the second group (Continued)

93	Woman	1.49
94	Woman	1.74
95	Woman	2.00
96	Woman	1.92
97	Woman	1.76
98	Woman	2.11
99	Woman	2.01
100	Woman	1.92
Average		2.114200
S. Deviation		0.649471

The mean FT4 hormone of female patients diagnosed with hypothyroidism in the second group was calculated as 0.97 ± 0.29, it is illustrated in Table 4.10. Although this mean value is within the reference value range, the lower limit of the reference values of 0.89 – 1.46 ng/dL is close to 0.89 ng/dL. This result reveals that although FT4 hormone levels of diabetic patients are in the lower reference range, FT4 deficiency, which is one of the markers of hypothyroidism, is observed in some diabetic patients and that the symptoms of hypothyroidism can be seen in diabetic patients, albeit partially. Although FT4 values are within the reference value range in some of the 50 female patients with diabetes, whom you have considered individually, it is seen that this value is below the 0.89 ng/dL value, which is a symptom of hypothyroidism, in some patients. In these results, the standard deviation can give an idea.

Table 4.10 Free T4 value statistics of female patients in the second group

Patient No	**Gender**	**FT4 (ng/dL)**
51	Woman	1.15
52	Woman	1.42
53	Woman	0.89
54	Woman	1.7
55	Woman	1.42
56	Woman	0.76
57	Woman	0.88
58	Woman	0.72
59	Woman	0.75
60	Woman	0.69

Table 4.10 FreeT4 value statistics of female patients in the second group (Continued)

61	Woman	1.57
62	Woman	0.85
63	Woman	0.76
64	Woman	0.76
65	Woman	1.61
66	Woman	0.87
67	Woman	0.76
68	Woman	0.81
69	Woman	0.71
70	Woman	0.82
71	Woman	0.8
72	Woman	1.52
73	Woman	0.81
74	Woman	0.79
75	Woman	1.62
76	Woman	0.99
77	Woman	1.12
78	Woman	0.71
79	Woman	0.89
80	Woman	0.82
81	Woman	0.8
82	Woman	0.89
83	Woman	1.12
84	Woman	1.66
85	Woman	1.14
86	Woman	0.94
87	Woman	0.77
88	Woman	0.81
89	Woman	0.89
90	Woman	0.79
91	Woman	1.43
92	Woman	1.22
93	Woman	0.72
94	Woman	0.69
95	Woman	0.91
96	Woman	0.81
97	Woman	0.84
98	Woman	0.88
99	Woman	0.85
100	Woman	0.72
Average		0.97700
S. Deviation		0.29977

The mean TSH hormone of female patients diagnosed with hypothyroidism in the second group was calculated as 4.84 ± 0.93, it is illustrated in Table 4.11. This mean value is higher than the upper limit of the reference values of 0.55–4.78 µU/mL, 4.78 µU/mL. This result shows that TSH hormone levels of diabetic patients are slightly above the lower reference value and reveals that TSH elevation, which is one of the markers of hypothyroidism, can be seen in diabetic patients. Although TSH values are within the reference value range in some of the 50 female patients with diabetes, whom you have considered individually, the group mean is slightly above the reference value.

Table 4.11 TSH value statistics of female patients in the second group

Patient No	**Gender**	**TSH (µU/ML)**
51	Woman	4.97
52	Woman	4.85
53	Woman	3.75
54	Woman	6.42
55	Woman	5.21
56	Woman	5.04
57	Woman	5.71
58	Woman	6.14
59	Woman	3.41
60	Woman	4.78
61	Woman	4.52
62	Woman	5.21
63	Woman	4.99
64	Woman	4.13
65	Woman	3.72
66	Woman	2.45
67	Woman	5.14
68	Woman	4.22
69	Woman	4.92
70	Woman	4.14
71	Woman	5.96
72	Woman	3.22
73	Woman	4.15
74	Woman	4.01
75	Woman	3.65
76	Woman	5.44
77	Woman	4.79
78	Woman	5.65

Table 4.11 TSH value statistics of female patients in the second group (Continued)

79	Woman	4.88
80	Woman	5.29
81	Woman	5.95
82	Woman	3.56
83	Woman	4.92
84	Woman	5.55
85	Woman	6.45
86	Woman	5.82
87	Woman	5.25
88	Woman	5.31
89	Woman	5.17
90	Woman	6.43
91	Woman	4.21
92	Woman	4.77
93	Woman	4.75
94	Woman	5.17
95	Woman	4.79
96	Woman	5.99
97	Woman	2.92
98	Woman	3.57
99	Woman	5.65
100	Woman	5.50
Average		4.849800
S. Deviation		0.936222

The mean serum glucose (Fasting blood sugar) of female patients diagnosed with hypothyroidism in the second group was calculated as 221.26 ± 87.144, it is illustrated in Table 4.12. This mean value is higher than the upper limit of the reference values of 74 – 106 mg/dL, 106 mg/dL. Considering that the patients in the second group had a confirmed diagnosis of diabetes, this is an expected result and in the second group this test was performed to confirm the diagnosis of diabetes.

Table 4.12 Serum glucose value statistics of female patients in the second group

Patient No	Gender	Serum glucose (mg/dL)
51	Woman	115
52	Woman	207
53	Woman	297
54	Woman	450
55	Woman	220
56	Woman	145
57	Woman	194
58	Woman	185
59	Woman	202
60	Woman	222
61	Woman	284
62	Woman	272
63	Woman	212
64	Woman	296
65	Woman	216
66	Woman	118
67	Woman	150
68	Woman	160
69	Woman	122
70	Woman	100
71	Woman	312
72	Woman	393
73	Woman	490
74	Woman	272
75	Woman	300
76	Woman	180
77	Woman	242
78	Woman	186
79	Woman	199
80	Woman	188
81	Woman	250
82	Woman	322
83	Woman	300
84	Woman	180
85	Woman	275
86	Woman	146
87	Woman	169
88	Woman	360
89	Woman	270
90	Woman	221
91	Woman	188

Table 4.12 Serum glucose value statistics of female patients in the second group (Continued)

92	Woman	99
93	Woman	175
94	Woman	287
95	Woman	163
96	Woman	200
97	Woman	112
98	Woman	177
99	Woman	150
100	Woman	90
Average		221.26000
S. Deviation		87.144422

In the second group, the mean diabetic hemoglobin test was calculated in female patients with hypothyroidism, it is illustrated in Table 4.13, and it was found that the percentage was high and indicative of diabetes, and some were susceptible to infection.

6.9738 ± 1.02. Note that the normal value is 4.2-6.5%. The fan average calculation is higher than the normal peak value.

Table 4.13 HbA1c statistics of female patients in the second group

Patient No	**Gender**	**HBA1C (%)**
51	Woman	7.8
52	Woman	8.9
53	Woman	6.1
54	Woman	5.6
55	Woman	7.8
56	Woman	6.9
57	Woman	6.4
58	Woman	7.8
59	Woman	6.4
60	Woman	6.9
61	Woman	8.1
62	Woman	6.2
63	Woman	5.4
64	Woman	5.9
65	Woman	6.8
66	Woman	7.8
67	Woman	6.8

Table 4.13 HbA1c statistics of female patients in the second group (Continued)

68	Woman	6.8
69	Woman	8.9
70	Woman	6.4
71	Woman	5.5
72	Woman	7.6
73	Woman	6.7
74	Woman	0.79
75	Woman	8.0
76	Woman	6.1
77	Woman	7.6
78	Woman	5.8
79	Woman	7.1
80	Woman	7.0
81	Woman	9.0
82	Woman	6.9
83	Woman	8.4
84	Woman	5.8
85	Woman	5.9
86	Woman	6.9
87	Woman	8.8
88	Woman	8.3
89	Woman	6.0
90	Woman	7.9
91	Woman	6.4
92	Woman	7.1
93	Woman	8.0
94	Woman	7.0
95	Woman	7.9
96	Woman	9.1
97	Woman	6.6
98	Woman	6.5
99	Woman	8.0
100	Woman	6.3
Average		6.9738
S. Deviation		1.02

The mean insulin value of women with hypothyroidism was calculated as 25.908 ± 1.45, it is illustrated in Table 4.14. Note that the normal insulin value is 2.6-24.9. The indication is that in some patients the mean calculation is high and in another normal.

Table 4.14 Insulin value statistics of female patients in the second group

Patient No	**Gender**	**Insulin (µU/ML)**
51	Woman	24.4
52	Woman	26.9
53	Woman	28.1
54	Woman	25.8
55	Woman	24.8
56	Woman	24.0
57	Woman	27.0
58	Woman	26.1
59	Woman	25.3
60	Woman	24.7
61	Woman	26.9
62	Woman	27.9
63	Woman	26.7
64	Woman	25.5
65	Woman	24.9
66	Woman	28.1
67	Woman	26.9
68	Woman	25.1
69	Woman	24.4
70	Woman	23.9
71	Woman	25.1
72	Woman	24.8
73	Woman	25.0
74	Woman	29.0
75	Woman	27.6
76	Woman	24.5
77	Woman	25.6
78	Woman	26.9
79	Woman	25.1
80	Woman	24.6
81	Woman	28.0
82	Woman	27.0
83	Woman	24.4
84	Woman	27.9
85	Woman	25.7
86	Woman	27.0
87	Woman	29.8
88	Woman	24.1
89	Woman	25.2
90	Woman	26.6
91	Woman	25.3

Table 4.14 Insulin value statistics of female patients in the second group (Continued)

92	Woman	25.0
93	Woman	24.7
94	Woman	26.7
95	Woman	23.8
96	Woman	26.0
97	Woman	25.1
98	Woman	26.7
99	Woman	23.7
100	Woman	27.1
Average		25.908
S. Deviation		1.45

5. CONCLUSION AND DISCUSSION

The most common endocrine disorders in the general population are diabetes and thyroid disorders. Among thyroid disorders, hypothyroidism is the most common worldwide. It has often been found to coexist with type 1 diabetes mellitus (T1DM) and T2DM. It is thought to be a triggering factor for hypoglycemia in diabetic patients. In addition, the incidence of hypothyroidism increases with age and is more common in women.

Among thyroid disorders, hypothyroidism is the most common worldwide. It has often been found to coexist with type 1 diabetes mellitus (T1DM) and T2DM. Hypothyroidism is at least twice as common in women as in men. Although hypothyroidism is most common in middle-aged or older women, the disease can occur at any age. In this study, middle-aged women (aged 45-65 years) were selected, who were previously diagnosed with hypothyroidism and did not have other chronic diseases. This study investigated the incidence of T1DM and T2DM in patients with pre-existing hypothyroidism and determined the incidence of hypothyroidism with pre-existing T1DM and T2DM. It has been observed that female patients between the ages of 45 and 65 who were diagnosed with hypothyroidism have a risk of developing diabetes. The risk of developing hypothyroidism in female patients aged 45–65 years diagnosed with diabetes was evaluated as positive based on the results of two of the three markers.

The main aim of this study was to evaluate the relationship between glucose levels and perceived age. We showed that diabetic subjects tended to have a higher perceived age compared to non-diabetic subjects. Also, in non-diabetic subjects, higher glucose levels were associated with higher perceived age, regardless of confounding factors. Comparison of assay results and statistics has been shown in Table 5.1 for the first group (hypothyroidism) and second group (diabetes) patients.

Table 5.1 Comparison of assay results and statistics of first group (hypothyroidism) and second group (diabetes) patients

Parameters	**First group (Hypothyroıdism)**	**Second group (Diabetes)**	**Reference value**	**Measurement units**
The average age	53.92 ± 7.01	55.30 ± 6.91	-	Year
Free T3	1.79 ± 0.44	2.11 ± 0.64	2.30 – 4.20	pg/ mL
Free T4	0.75 ± 0.19	0.97 ± 0.29	0.89 – 1.76	ng/dL
TSH	5.64 ± 0.76	4.89±0.93	0.55 – 4.78	µU/mL
Serum glucose (Fasting)	133.18 ± 57.62	221.26 ± 87.14	74 – 106	mg/dL
HbA1c	7.23± 0.75	6.9738 ± 1.02	4.2-6.5	%
Insulin	26.142 ± 1.31	25.908 ± 1.45	2.6-24.9	µU/mL

As seen in Table 5.1:

1. Hypothyroid patients give results compatible with the criteria of low FT3, low FT4 and high TSH, which are hypothyroid markers. This result confirms the diagnosis of hypothyroidism in Group I patients.

2. Hypothyroid patients give results compatible with high blood sugar (fasting blood sugar / serum glucose) value, which is a Diabetes marker. This result shows that there is a risk of diabetes for patients with hypothyroidism.

3. Diabetes patients give results compatible with High blood sugar (fasting blood sugar / serum glucose) value, which is a marker of diabetes. This conclusion confirms the diagnosis of diabetes in the second group of patients.

4. Diabetes patients give results compatible with the criterion of low FT3 value, which is a marker of hypothyroidism.

5. Diabetes patients give results partially compatible with low FT4 value, which is a marker of hypothyroidism. When the average values of the second group are examined, it is seen that the group average of the diabetic patients is in the FT4 reference value range, but when the individual results are examined, it is seen that the diabetes patients have low FT4 hormone.

6. Diabetes patients give results consistent with high TSH value, which is a marker of hypothyroidism.

7. Diabetes (HbA1c) and high insulin levels are indicators of diabetes.

5.1 Conclusion

1. It is seen that female patients between the ages of 45 and 65 who have been diagnosed with hypothyroidism have a risk of developing Diabetes.
2. Female patients aged 45-65 years diagnosed with diabetes are at risk of developing hypothyroidism, and are evaluated positively based on the results of two of the three markers.

REFERENCES

Akbar, D. H., Ahmed, M. M. and Al-Mughales, J. 2006. Thyroid dysfunction and thyroid autoimmunity in Saudi type 2 diabetics. Acta Diabetologica, 43, 14-18.

Barbesino, G. 2010. Drugs affecting thyroid function. Thyroid, 20, 763–770.

Barker, J.M., Yu, J. and Yu, L., 2005. Autoantibody "subspecificity" in type 1 diabetes: risk for organ-specific autoimmunity clusters in distinct groups. Diabetes Care, 28, 850–855.

Baxter, J. D. and Webb, P. 2009. Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. Nature Reviews Drug Discovery, 8, 308-320.

Baxter, J. D., Dillmann, W. H., West, B. L., Huber, R., Furlow, J. D., Fletterick, R. J. and Scanlan, T.S. 2001. Selective modulation of thyroid hormone receptor action. The Journal of Steroid Biochemistry and Molecular Biology, 76, 31-42.

Beylot, M., Riou, J. P., Bienvenu, F. and Mornex R., 1980. Increased ketonaemia in hyperthyroidism. Evidence for a β-adrenergic mechanism. Diabetologia, 19, 505–510.

Boelen, A., 2009. Thyroid hormones and glucose metabolism: the story begins before birth. Experimental Physiology, 94, 1050–1051.

Brenta G., Danzi S. and Klein I. 2007. Potential therapeutic applications of thyroid hormone analogs. Nature Clinical Practice Endocrinology and Metabolism, 3, 632–640.

Brenta, G., Celi F. S., Pisarev M., Schnitman M., Sinay I. and Arias P. 2009. Acute thyroid hormone withdrawal in athyreotic patients results in a state of insulin resistance. Thyroid, 19, 665–669.

Canaris, G. J., Manowitz, N. R., Mayor, G. and Ridgway, E. C. 2000. The Colorado thyroid disease prevalence study. Archives of Internal Medicine, 160, 526-534.

Cavallo-Perin, P., Bruno, A., BOINE, L., Cassader, M., Lenti, G. and Pagano, G. 1988. Insulin resistance in Graves' disease: a quantitative invivo evaluation. European Journal of Clinical Investigation, 18, 607-613.

Chen, G., Wu, J., Lin, Y., Huang, B., Yao, J., Jiang, Q. and Lin, L. 2010. Associations between cardiovascular risk, insulin resistance, β -cell function and thyroid dysfunction: a cross-sectional study in She ethnic minority group of Fujian Province in China. Eur J Endocrinol, 163, 775-782.

Coller, F. A. and Huggins, C. B. 1927. Effect of hyperthyroidism upon diabetes mellitus: striking improvement in diabetes mellitus from thyroidectomy. Annals of Surgery, 86, 877–884.

de Lange, P., Feola, A., Ragni, M., Senese, R., Moreno, M., Lombardi, A. and Lanni, A. 2007. Differential 3, 5, 3′-triiodothyronine-mediated regulation of uncoupling protein 3 transcription: role of fatty acids. Endocrinology, 148, 4064-4072.

DeFronzo, R. A., Gunnarsson, R., Björkman, O., Olsson, M. and Wahren, J. 1985. Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. The Journal of Clinical Investigation, 76, 149-155.

DeFronzo, R. A. 2004. Pathogenesis of type 2 diabetes mellitus. Medical Clinics of North America. 88, 787–835.

Dimitriadis, G., Baker, B., Marsh, H., Mandarino, L., Rizza, R., Bergman, R. and Gerich, J. 1985. Effect of thyroid hormone excess on action, secretion, and metabolism of insulin in humans. American Journal of Physiology-Endocrinology And Metabolism, 248, E593-E601.

Dimitriadis, G., Mitrou, P., Lambadiari, V., Boutati, E., Maratou, E., Panagiotakos, D. B., and Raptis, S. A. 2006. Insulin action in adipose tissue and muscle in hypothyroidism. The Journal of Clinical Endocrinology and Metabolism, 91, 4930-4937.

Dimitriadis, G., Mitrou, P., Lambadiari, V., Boutati, E., Maratou, E., Koukkou, E. and Raptis, S. A. 2008. Insulin-stimulated rates of glucose uptake in muscle in hyperthyroidism: the importance of blood flow. The Journal of Clinical Endocrinology and Metabolism, 93, 2413-2415.

Duntas, L. H., Orgiazzi, J. and Brabant, G. 2011. The interface between thyroid and diabetes mellitus. Clinical Endocrinology, 75, 1-9.

Eledrisi, M. S., Alshanti, M. S., Shah, M. F., Brolosy, B. and Jaha, N. 2006. Overview of the diagnosis and management of diabetic ketoacidosis. The American Journal of the Medical Sciences, 331, 243-251.

Freake, H. C. and Oppenheimer, J. H. 1987. Stimulation of S14 mRNA and lipogenesis in brown fat by hypothyroidism, cold exposure, and cafeteria feeding: evidence supporting a general role for S14 in lipogenesis and lipogenesis in the maintenance of thermogenesis. Proceedings of the National Academy of Sciences, 84, 3070-3074.

Garber, J. R., Cobin, R. H, Gharib, H., Hennessey, J. V., Klein, I. and Mechanick, J. I. 2012. American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocrine Practice, 18, 988–1028.

Gauthier, K., Billon, C. and Bissler M. 2010. Thyroid hormone receptor β(TRβ) and liver X receptor (LXR) regulate carbohydrate-response element-binding protein (ChREBP) expression in a tissue-selective manner. Journal of Biological Chemistry, 285, 28156–28163.

Goglia, F., Moreno, M. and Lanni, A. 1999. Action of thyroid hormones at the cellular level: the mitochondrial target. FEBS Letters, 452, 115-120.

Hage M., Zantout M.S. and Azar, S.T. 2011. Thyroid disorders and diabetes mellitus. Journal Thyroid Research, 34, 439-463.

Handisurya, A., Pacini, G., Tura, A., Gessl, A. and Kautzky W., A. 2008. Effects of T4 replacement therapy on glucose metabolism in subjects with subclinical (SH) and overt hypothyroidism (OH). Clinical Endocrinology, 69, 963-969.

Harris, P. E., Walker, M., Clark, F., Home, P. D. and Albert, K. 1993. Forearm muscle metabolism in primary hypothyroidism. European journal of clinical investigation, 23, 585-588.

Holl, R. W., Bohm, B., Loos, U., Grabert, M., Heinze, E. and Homoki, J. 1999. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. Hormone Research in Paediatrics, 52, 113-118.

Hollowell, J. G., Staehling, N. W., Flanders, W. D., Hannon, W. H., Gunter, E. W., Spencer, C. A. and Braverman, L. E. 2002. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition

Examination Survey (NHANES III). The Journal of Clinical Endocrinology and Metabolism, 87, 489-499.

Indra, R., Patil, S. S., Joshi, R., Pai, M. and Kalantri, S. P. 2004. Accuracy of physical examination in the diagnosis of hypothyroidism: a cross-sectional, double-blind study. Journal of Postgraduate Medicine, 50, 7-11.

Kadiyala, R., Peter, R. and Okosieme, O. E. 2010. Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. International Journal of Clinical Practice, 64, 1130-1139.

Kalmann, R. and Mourits, M. P. 1999. Diabetes mellitus: a risk factor in patients with Graves' orbitopathy. British Journal of Ophthalmology, 83, 463-465.

Kalra, S., Unnikrishnan, A. G. and Sahay, R. 2014. The hypoglycemic side of hypothyroidism. Indian Journal of Endocrinology and Metabolism, 18, 1-3.

Klieverik, L. P., Coomans, C. P., Endert, E., Sauerwein, H. P., Havekes, L. M., Voshol, P. J. and Fliers, E. 2009. Thyroid hormone effects on whole-body energy homeostasis and tissue-specific fatty acid uptake in vivo. Endocrinology, 150, 5639-5648.

Klieverik, L. P., Janssen, S. F., van Riel, A., Foppen, E., Bisschop, P. H., Serlie, M. J. and Kalsbeek, A. 2009. Thyroid hormone modulates glucose production via a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver. Proceedings of the National Academy of Sciences, 106, 5966-5971.

Kordonouri, O., Maguire, A. M., Knip, M., Schober, E., Lorini, R., Holl, R. W. and Donaghue, K. C. 2009. Other complications and associated conditions with diabetes in children and adolescents. Pediatric Diabetes, 10, 204-210.

Levin, R. J. and Smyth, D. H. 1963. The effect of the thyroid gland on intestinal absorption of hexoses. The Journal of physiology, 169, 755–769.

Lindberg, B., Ericsson, U. B., Ljung, R. and Ivarsson, S. A. 1997. High prevalence of thyroid autoantibodies at diagnosis of insulin-dependent diabetes mellitus in Swedish children. Journal of Laboratory and Clinical Medicine, 130, 585-589.

Mandarino, L., Bonadonna, R., McGuinness, O. and Wasserman D. 2001. Regulation of muscle glucose uptake in vivo. In: Jefferson LS, Cherrington AD, editors. Handbook of Physiology, The Endocrine System, The Endocrine Pancreas and Regulation of Metabolism. Oxford, UK: Oxford University Press, 32, 803-848.

Mari, A., Wahren, J., DeFronzo, R. A. and Ferrannini, E. 1994. Glucose absorption and production following oral glucose: comparison of compartmental and arteriovenous-difference methods. Metabolism, 43, 1419-1425.

Matty, A. J. and Seshadri, B., 1965. Effect of thyroxine on the isolated rat intestine. Gut, 6, 200-202.

Menconi, F., Osman, R., Monti, M. C., Greenberg, D. A., Concepcion, E. S. and Tomer, Y. 2010. Shared molecular amino acid signature in the HLA-DR peptide binding pocket predisposes to both autoimmune diabetes and thyroiditis. Proceedings of the National Academy of Sciences, 107, 16899-16903.

Miki, N., Ono, M., Hizuka, N., Aoki, T. and Demura, H. 1992. Thyroid hormone modulation of the hypothalamic growth hormone (GH)-releasing factor-pituitary GH axis in the rat. The Journal of Clinical Investigation, 90, 113-120.

Moeller, L. C., Dumitrescu, A. M., Walker, R. L., Meltzer, P. S. and Refetoff, S. 2005. Thyroid hormone responsive genes in cultured human fibroblasts. The Journal of Clinical Endocrinology and Metabolism, 90, 936-943.

Moreno, M., Silvestri, E., De Matteis, R., de Lange, P., Lombardi, A., Glinni, D., Senese, R., Cioffi, F., Salzano, A. M., Scaloni, A., Lanni, A. and Goglia, F. 2011. 3, 5-Diiodo-L-thyronine prevents high fat-diet-induced insulin resistance in rat skeletal muscle through metabolic and structural adaptations. The FASEB Journal, 25, 3312-3324.

Mouradian, M. and Abourizk, N. 1983. Diabetes mellitus and thyroid disease. Diabetes Care, 6, 512-520.

Muoio, D. M. and Newgard, C. B. 2008. Mechanisms of disease: molecular and metabolic mechanisms of insulin resistance and β-cell failure in type 2 diabetes. Nature Reviews Molecular Cell Biology, 9, 193–205.

O'Meara, N. M., Blackman, J. D., Sturis, J. and Polonsky, K. S. 1993. Alterations in the kinetics of C-peptide and insulin secretion in hyperthyroidism. The Journal of Clinical Endocrinology and Metabolism, 76, 79-84.

Owecki, M., Nikisch, E. and Sowiński, J. 2006. Hypothyroidism has no impact on insulin sensitivity assessed with HOMA-IR in totally thyroidectomized patients. Acta Clinica Belgica, 61, 69-73.

Ozair, M., Noor, S., Raghav, A., Siddiqi, S. S., Chugtai, A. M. and Ahmad, J. 2018. Prevalence of thyroid disorders in North Indian Type 2 diabetic subjects: A cross sectional study. Diabetes and Metabolic Syndrome: Clinical Research and Reviews, 12, 301-304.

Peppa, M., Betsi, G. and Dimitriadis, G. 2011. Lipid abnormalities and cardiometabolic risk in patients with overt and subclinical thyroid disease. Journal of Lipids, 9, 575-584.

Potenza, M., Via, M. A. and Yanagisawa, R. T. 2009. Excess thyroid hormone and carbohydrate metabolism. Endocrine Practice, 15, 254-262.

Rezzonico, J., Niepomniszcze, H., Rezzonico, M., Pusiol, E., Alberto, M. and Brenta, G. 2011. The association of insulin resistance with subclinical thyrotoxicosis. Thyroid, 21, 945-949.

Rezzonico, J., Rezzonico, M., Pusiol, E., Pitoia, F. and Niepomniszcze, H. 2008. Introducing the thyroid gland as another victim of the insulin resistance syndrome. Thyroid, 18, 461-464.

Rochon, C., Tauveron, I., Dejax, C., Benoit, P., Capitan, P., Fabricio, A., Berry, C., Champredon , C., Thieblot , P. and Grizard, J. 2003. Response of glucose disposal to hyperinsulinaemia in human hypothyroidism and hyperthyroidism. Clinical Science, 104, 7-15.

Ross, D., Cooper, D., & Mulder, J. 2019. Diagnosis of and screening for hypothyroidism in nonpregnant adults. UpToDate, 7893, 1-24.

Saluja, M., Pyarsabadi, P., Jelia, S., Chittora, S., Swami, Y. and Vimlani, H. 2018. Study of thyroid dysfunction in metabolic syndrome and association with its components. Current Medicine Research and Practice, 8, 3-7.

Shen, D. C., Davidson, M. B., Kuo, S. W. and Sheu, W. 1988. Peripheral and hepatic insulin antagonism in hyperthyroidism. The Journal of Clinical Endocrinology and Metabolism, 66, 565-569.

Stanická, S., Vondra, K., Pelikánová, T., Vlček, P., Hill, M. and Zamrazil, V. 2005. Insulin sensitivity and counter-regulatory hormones in hypothyroidism and during thyroid hormone replacement therapy. Clinical Chemistry and Laboratory Medicine (CCLM), 43, 715-720.

Tosi, F., Moghetti, P., Castello, R., Negri, C., Bonora, E. and Muggeo, M. 1996. Early changes in plasma glucagon and growth hormone response to oral glucose in experimental hyperthyroidism. Metabolism, 45, 1029-1033.

Tunbridge, W. M. G., Evered, D. C., Hall, R., Appleton, D., Brewis, M., Clark, F. and Smith, P. A. 1977. The spectrum of thyroid disease in a community: the Whickham survey. Clinical Endocrinology, 7, 481-493.

Wang, C. 2013. The relationship between type 2 diabetes mellitus and related thyroid diseases. Journal of Diabetes Research, 3, 521-534.

Weinstein, S. P., O'Boyle, E. and Haber, R. S. 1994. Thyroid hormone increases basal and insulin-stimulated glucose transport in skeletal muscle: the role of GLUT4 glucose transporter expression. Diabetes, 43, 1185-1189.

Weitzel, J. M., Radtke, C. and Seitz, H. J. 2001. Two thyroid hormone-mediated gene expression patterns in vivo identified by cDNA expression arrays in rat. Nucleic Acids Research, 29, 5148-5155.

Zaletel, K. and Gaberscek, S. 2011. Hashimoto's thyroiditis: from genes to the disease. Current Genomics, 12, 576-588.

CURRICULUM VITAE

Personal Information

Name and Surname : Marwan Sami Abdulhussein AL-TAMEEMI

Education

MSc	Çankırı Karatekin University Graduate School of Natural and Applied Sciences Department of Chemistry	2019-Present
Undergraduate	Al-Mustansiriya University College of Science Department of Chemistry	1998-2002