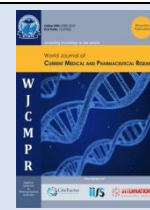




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## GENERAL OVERVIEW OF THE RISK FACTORS, PATHOGENESIS, AND COMBINED TREATMENTS FOR HASHIMOTO'S THYROIDITIS (HT)

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| Article History                                                                    | Abstract                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| Received on: 21-07-2023<br>Revised on: 04-08-2023<br>Accepted on: 18-09-2023       | In regions of the world where iodine is abundant, Hashimoto's thyroiditis, also known as Hashimoto's disease or autoimmune thyroiditis, is the most prevalent cause of hypothyroidism. It is a chronic inflammation of the thyroid gland. It is characterized by autoimmune-mediated thyroid gland destruction, which results in progressive thyroid failure, either with or without goitre formation. In young to middle-aged women, Hashimoto's thyroiditis typically starts as a painless, diffuse, firm thyroid gland enlargement those progresses to hypothyroidism. Many people don't initially exhibit hypothyroidism, and some don't even have goitre or may have an atrophic thyroid gland. Hashimoto's thyroiditis (HT), also known as chronic autoimmune thyroiditis, is an inflammatory condition that is characterized by parenchymal atrophy, fibrosis, and diffuse lymphocytic infiltration. Being the main source of primary hypothyroidism in regions with adequate iodine. With the help of various criteria, such as physical examination, blood tests for thyroid hormone levels (TSH is low, T3 and T4 are tall, for example), serum cholesterol and triglycerides, blood glucose, and radioactive iodine uptake, it is possible to distinguish between infections and clutter. According to estimates from several thyroid disease studies, 42 million persons in India are estimated to have the ailment. The pathogenesis, causes, risk factors and combination therapy linked to Hashimoto's thyroiditis are discussed in this review study. |
|  | <b>Keywords:</b> Hashimoto's thyroiditis, Etiology, Epidemiology, Risk factors, Signs and Symptoms, Pathophysiology, Treatments.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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### Introduction

Due to a decline in immunologic tolerance to immune cells that are prone to auto-reactivity, thyroid disease is brought on when the immune system starts attacking its own molecules. Autoimmune illnesses frequently attack the thyroid gland, which is prone to hypothyroidism, lymphocytic thyroiditis (Hashimoto's thyroiditis), and hyperthyroidism (Graves' disease) [1,2]. The hypothalamus, pituitary gland, and thyroid gland control the production of thyroid hormones. In tropical regions, the hypothalamus secretes thyrotrophic-releasing hormones (TRH), which cause the pituitary gland to release thyroid-stimulating hormones (TSH). TSH works hardest to target and increase thyroid hormone production. Thyroid

hormones increase the body's ability to digest food and use oxygen, have calorie-burning effects, and stimulate the central nervous system while also promoting growth and mobility. Thyroxine (T4) and triiodothyronine (T3) are the two most important thyroid hormones. T3 hormone is the most often used hormone that serves as an organic control [3]. Auto-antigens found in the thyroid gland trigger an inappropriate immune response that results in thyroid disorders. Hypothyroidism, lymphocytic thyroiditis (Hashimoto's thyroiditis), and hyperthyroidism are the three main autoimmune thyroid disorders. The thyroid gland is underactive and generates too little thyroid hormone when someone has hypothyroidism. A hoarse voice, slurred speech, pudgy face, drooping eyelids, intolerance to cold weather, constipation, weight gain, dry skin, dry hair, and depression are typical signs of hypothyroidism. Cardiovascular disease, osteoporosis, being overweight, celiac disease, and diabetes are all more common among hypothyroid patients [4,5]. According to estimates, 0.2% of men and 2% of women globally suffer from thyroid illness. Stress, heavy metal and hazardous chemical exposure, and tobacco use can all considerably raise

the risk of thyroid diseases [6–9]. The prevalence of thyroid disease is significantly higher in older people than in younger people, and it might also be hidden because of concomitant conditions. Children can also be affected by thyroid problems, which are typically detected in people between the ages of 45 and 65 [10]. In 1912, Dr. Hakuru Hashimoto published the first description of Hashimoto's thyroiditis. The term "Struma Lymphomatosa" was first coined by Hashimoto based on the histology results. Lymphocytic thyroiditis, autoimmune thyroiditis, chronic thyroiditis, and lymph adenoid goitre are some of the names that this condition has gone by over time [11]. Hakaru Hashimoto, a Japanese doctor, initially defined Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis or Hashimoto's illness, as an enlarged thyroid with a persistent lymphatic infiltration, in 1912. The hypertrophic or goitrous form of HT is another name for this type of HT that is widely used. A secondary atrophic form of HT usually results from the thyroid shrinking over many years. Ord thyroiditis is characterized by a thyroid gland that is normal or diminished in size at the time of diagnosis and a lymphatic infiltration. Nevertheless, in clinical practise, Hashimoto's thyroiditis (HT) is frequently used to refer to these many types of HT [12]. An autoimmune condition known as Hashimoto's thyroiditis (HT) occurs when the thyroid is attacked by the body's immune system. It will eventually result in the clinical condition known as hypothyroid, which will be caused by a decrease in thyroid activity. Patients with untreated hypothyroidism may experience mild to severe symptoms such as weight gain, depression, constipation, brain fog, exhaustion, hair loss, cold sensitivity, sleep difficulties, goitres (thyroid gland enlargement), and thyroid cancer. Women are 10–20 times as likely than males to get HT illness [5,13,14]. The onset of hypothyroidism, hypovitaminosis D2, and, sometimes, thyroid storm are the problems that are most frequently mentioned. The relationship with other autoimmune disorders, such as autoimmune pancreatitis, Sjögren's syndrome, and steroid responsive encephalopathy, has also been shown to exist. Through its effects on regional and systemic hemodynamics, hypothyroidism can have an indirect or direct impact on renal physiology [15]. Both the genetic and environmental components contribute to the development of HT. In practically every patient with autoimmune hypothyroidism, circulating autoantibodies against thyroglobulin and thyroid peroxidase (TPO) have been discovered. Thyroid-stimulating hormone receptor antibodies (TSH-R Ab) are also present in some cases of HT, blocking the receptor rather than activating it as in Graves' illness [16]. The most common cause of hypothyroidism, HT affects the central nervous system, growth and development, the cardiovascular system (CVS), the skeletal system, the gastrointestinal tract (GIT), and reproductive activities in 4-9.5% of adults. For the diagnosis of HT, several biochemical diagnostic tests are available, including the free tetraiodothyronine (T4) hormone test, antithyroid antibody testing, and the thyroid-stimulating hormone (TSH) test. The HT can be treated using a variety of medical approaches, including allopathic and natural medications [17–20]. More frequently impacted are women. At least ten to one is the ratio of women to men. Most women are diagnosed between the ages of 30 and 50, while some sources

claim that this is when it happens more frequently. Levothyroxine at the recommended dose of 1.6 to 1.8 mcg/kg/day makes up the standard of care. The T4 is converted to T3, which is the human body's active form of thyroid hormone. The diagnosis can be difficult and delayed until the disease has progressed further. The most frequent test results show increased thyroid-stimulating hormone (TSH) levels, low levels of free thyroxine (fT4), and raised antithyroid peroxidase (TPO) antibodies. However, patients may display symptoms, indications, and laboratory results consistent with hyperthyroidism or normal levels earlier in the course of the disease. This is due to the possibility of intermittent thyroid gland cell death [21,22].

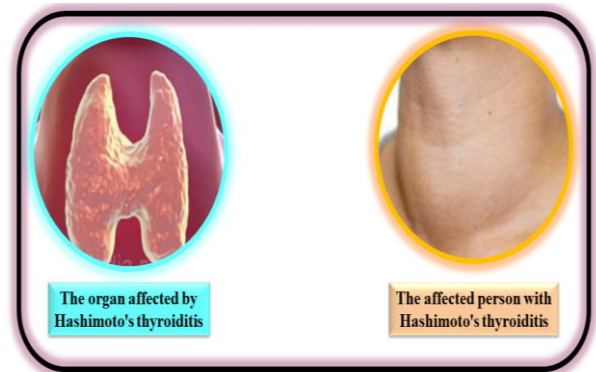


Fig.1: Hashimoto's thyroiditis disease.

### Etiology

The thyroid gland is invaded and destroyed by lymphocytic cells that have been triggered by the autoimmune system. The pathogenesis of HT is significantly influenced by excessively excited T CD4+ cells, those cells' differentiated cells (ThH1, Th2, Th17, and Treg), and other proinflammatory cytokines like interferon and interleukin (IL) [17]. The underlying causes of the pathological autoimmune reaction to the thyroid gland are thought to be multifaceted, with environmental factors including the amount of iodine available, infections, and stress acting as immune modulation triggers. Additionally, it has been suggested that the gut microbiome may influence thyroid immunology and the emergence of HT [23–27]. A multistep process including genetic, immunological, and environmental elements leads to the HT disease. When immune tolerance is lost, the normal thyroid cells stimulate the development of antibodies against thyroid tissue, which destroys the thyroid gland if it is large. Thyroglobulin is thought to be produced by thyroid tissue [28]. It is reported that thyroglobulin proteins have roughly 40 different type of epitope, which has a participation in the pathogenesis of HT [29]. Additionally, the HLA gene, several immunoregulatory genes (CD25, CD40, FOXP3, CTLA4, PTPN22), and thyroid-specific genes (thyroid stimulating hormone receptor, thyroglobulin) all play important roles in this process. The thyroid gland decreases due to the cumulative organ damage caused by activated macrophages and cytotoxic lymphocytes, which frequently results in hypothyroidism over time. As a result, the primary goal of HT treatment is to manage thyroid insufficiency with oral L-thyroxine replacement. However, HT patients frequently report a wide range of symptoms, some of which are scarcely fully explicable by HT alone [30].

## Epidemiology

In the United States and those regions of the world where iodine consumption is adequate, Hashimoto is the most frequent cause of hypothyroidism beyond the age of six. According to estimates, the incidence for men is 0.8 per 1000 per year and for women it is 3.5 per 1000 per year. According to twin research, monozygotic twins have a higher concordance of autoimmune thyroiditis than dizygotic twins. Danish research have shown that monozygotic twin concordance rates are 55%, while dizygotic twin concordance rates are barely 3%. According to the study, genetic variables account for 79% of propensity, leaving 21% to environmental and sex hormone influences. In general, thyroid disease is more common as people age [31]. 42 million people in India are thought to have thyroid disease, based on projections from several research on the condition(32).In India, 11% of people have hypothyroidism, compared to 2% in the UK and 46% in the USA. Cities located inland, such as Kolkata, Delhi, Ahmedabad, Bangalore, and Hyderabad, have a greater prevalence (117% vs 95%), compared to coastal cities (such as Mumbai, Goa, and Chennai). Ambrish Mithal, chairman of the Medanta Division of Endocrinology and Diabetes in Gurgaon, India, believes that the country's long-standing iodine deficiency, which has only partially been remedied over the past 20 years, may be the cause of India's higher mean thyroid hormone stimulation glucose range and concentration than that of western nations. People between the ages of 46 and 54 have the highest frequency of hypothyroidism (13 %), whereas those between the ages of 18 and 35 have a lower incidence (7 %) [33].

## Risk Factors

The likelihood of thyroid diseases has been linked to a number of factors, including gender, exposure to hazardous chemicals and heavy metals, gluten, and stress. Most thyroid conditions affect women more frequently than they do men. Only during puberty can sex-specific changes in the microbiome composition emerge(4).The sex hormones and the existence of two X chromosomes as opposed to one X and one Y chromosome are the primary differences between the immune systems of males and females. In the early stages of embryogenesis in females, one of the X chromosomes is randomly silenced in order to prevent double dosage of X chromosome-derived proteins. Some X-linked genes are overexpressed in females due to incomplete X chromosomal inactivation, which leaves 15% of the genes active(34,35).Additionally, sex hormones like oestrogen, progesterone, androgens, as well as pro-lectin, may have an impact on many immune system functions as well as the risk, activity, and development of thyroid illnesses.This is because immune cells have hormone receptors.In general, testosterone and progesterone serve as naturally occurring immune suppressants, but oestrogens, especially 17- $\beta$  estradiol (E2) and prolactin, act as boosters at least of humeral immunity. In particular, prolactin stimulates the synthesis of pro-inflammatory cytokines, controls CD4+ T cell growth, and boosts antibody production [9,36,37]. Smoking tobacco is a risk factor for the onset of systemic lupus erthematosus, with a ratio of 1.5 between those who now smoke and those who have never smoked. Smoking results in tissue damage and increases

apoptosis due to free radical production that is high, metalloproteinase release, and activation of Fas expression on lymphocytes, which is linked to the creation of autoantibodies. Smoking also increases levels of fibrinogen, causes leucocytosis, and raises levels of C-reactive protein, intercellular adhesion molecule-I, and E-selectin, all of which contribute to inflammation [8,38]. The neurological and endocrine systems can directly or indirectly impact the immune system due to stress. The acute phase response, which is a component of the innate immune inflammatory response, is activated by stressful conditions and the body releases cortisol as a result. When under stress, the hypothalamic-pituitary-adrenal axis and sympathoadrenal system become activated, which increases the release of glucocorticoids and catecholamines, respectively. Stress-induced neuroendocrine hormones may cause immunological dysregulation or increase cytokine production, which might result in atopic thyroid disease. Additionally, stress hormones may affect the differentiation of bipotential helper T-cells away from an H1 phenotype and towards an H2 phenotype by acting on antigen-presenting immune cells [6,39,40].

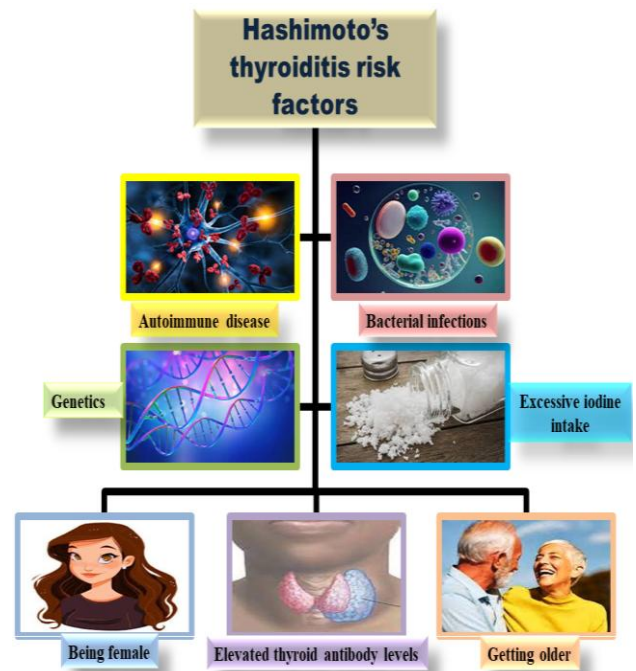


Fig.2: Hashimoto's thyroiditis illness Risk factors.

## Sign and Symptoms

The thyroid gland follicle-containing glycoprotein thyroglobulin, which is created by iodinating tyrosine residues, is where thyroid hormone is made. Thyroid hormone's main function is to control basal metabolic rate. The main signs of HT include the death of thyroid tissue, which results in reduced thyroid hormone output and a slowing in metabolic activity. In the early stages of the illness, the TSH level does not fluctuate substantially. The decreased thyroid hormone output also has negative effects on a variety of other organ systems. Some of these include bradycardia, which is a CVS dysfunction sign; delayed reflexes and slurred speech; these are nervous system dysfunction symptoms; constipation; enhanced bile reflex; and acites; these are gastrointestinal dysfunction symptoms [41–43]. Body weight increased as a result of fluid retention and a decreased metabolism. Myxedema is caused by hypoglycemia,

altered sensorium, and severe bradycardia. Traumatic injuries, infection, and surgery are the main causes of myxedema. Rheumatic illness and autoimmune disorders might occasionally also impact HT. Additionally, after HT was diagnosed in a patient, depression, irritability, weariness, and bewilderment have occasionally been noted as first symptoms [44].

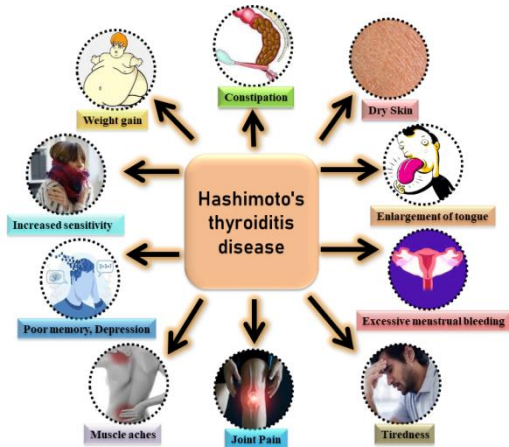


Fig.3: Symptoms and signs of Hashimoto's thyroiditis.

### Pathophysiology

Hashimoto's thyroiditis is the result of a multi-step, complex pathophysiology that is influenced by a number of genetic, environmental, and immunological variables. In a nutshell, when the immune system no longer tolerates normal thyroid cells, antibodies are produced that are specific for thyroid tissue, which results in the death of the thyroid gland. When individuals who are genetically susceptible are exposed to the aforementioned environmental conditions, the early inflammatory alterations in the illness process are started. After the initial inflammatory phase, dendritic cells and macrophages, which are MHC class 2 antigen-presenting cells, infiltrate the thyroid gland. Cells deliver the thyroid gland autoantigen components to the immune system for processing. Thyroglobulin, the primary protein generated in thyroid tissue, is thought to have a key role in the pathophysiology of this disease among a wide range of possible auto-antigens [28]. According to reports, the thyroglobulin protein has about 40 different types of epitopes, each of which is crucial to the pathophysiology of the disease. The epitope recognition pattern of the antibodies in autoimmune thyroid disease is different from that of healthy people, inducing immunological and inflammatory processes [29,45]. An important role in the pathophysiology of the disease is also played by thyroid peroxidase, an enzyme that catalyzes the oxidation of iodine. Additionally, 180 distinct subtypes of thyroid peroxidase antibodies have so far been discovered. The production of autoreactive cells directed towards the thyroid gland, which could stem from deficiencies in central tolerance or defects in the sodium iodide symporter, is the key step in the pathophysiology of thyroid disease, according to studies. tolerance on the periphery. Loss of immunological tolerance has been linked to hereditary immune abnormalities or a deficiency in the regulatory T-cells that impose the suppression of activity [46]. Self-reactive T-lymphocytes and B-lymphocytes then develop, clonal expand, and mature in

the draining lymph nodes. The core phase of autoimmunity, which is the next step, is characterized by the unchecked synthesis of self-reactive cells and auto antibodies in response to the presenting antigens. Initially, this process takes place in the lymph nodes, but as the illness worsens, the thyroid gland becomes the new site of production, and lymphoid tissue then develops there. Anti-thyroid peroxidase (ATPO) and anti-thyroglobulin (TGAB) antibodies, which are directed towards thyroid cells, are produced by the activated B-lymphocytes. The thyroid gland is infiltrated by autoreactive T-cells produced during the illness phase, which then mediate the thyroid glands demise by cytotoxicity with the help of CD+8 cells. When macrophages are stimulated in this way, they create a large number of cytokines that, when combined with antibodies, start the process of tissue death. Final stage of the process involves the induction of thyroid gland-destructive enzymes by caspases, which are self-activated through proteolytic cleavage. In a healthy thyroid gland, the creation of new cells and the degeneration of old cells are strictly regulated such that there is always a preponderance of functional cells. Control over the thyroid glands cells being destroyed is lost as the condition progresses. One of the elements that significantly contribute to the deregulation of the thyroid glands normal destructive functions is genetic vulnerability. Initiating the apoptosis process depends on a number of other stimuli that affect the production of Bcl-2, the apoptosis inhibitor, or FasL membrane ligand [47]. When compared to normal thyroid cells, thyroid cells in tissue afflicted by Hashimoto's thyroiditis are capable of expressing more FasL proteins, which speeds up the rate of apoptosis. The rate of thyroid gland apoptosis determines the severity of the condition and the clinical result. Expression of these proteins is directly correlated with disease severity, and as the rate of apoptosis rises, less hormonally active thyroid tissue is present, which reduces thyroid hormone synthesis and causes more severe disease signs [48].

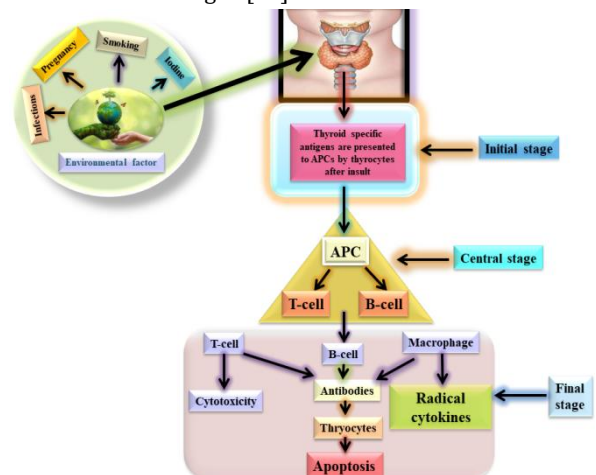


Fig.4: Hashimoto's thyroiditis's pathophysiology [11].

### The Identification of Hashimoto's Thyroiditis (HT)

Accurate diagnosis of Hashimoto's thyroiditis depends greatly on determining the patient's metabolic status and the type of lesion present. Assessing thyroid hormone status, which shows glandular function, should be the initial step. Goitre alone, without accompanying hyperthyroid symptoms, is suggestive of Hashimoto's thyroiditis, while goitre in a patient with hypothyroidism is highly believed to be symptomatic of

Hashimoto's thyroiditis. The most widely used lab tests to determine the level of thyroid gland function are the levels of triiodothyronine (T3), tetraiodothyronine (T4), and thyroid stimulating hormone (TSH). TSH has been identified as the most sensitive indicator of hypothyroidism among these variables. Even after the diagnosis has been made, the TSH is routinely checked to gauge the disease's course and response to treatment. The determination of the presence of antithyroid antibodies comes next after the evaluation of the patient's thyroid function status. It should be noted that although antithyroglobulin (TGAB) and antithyroid peroxidase (ATPO) antibodies are both positively connected with Hashimoto's thyroiditis, TGAB has a marginally stronger correlation than ATPO [17]. Antithyroid antibodies would suggest underlying lymphocytic infiltration of the gland and be symptomatic of autoimmune illness even in the absence of hypothyroid symptoms. Anti-microsomal antibodies have been proven to provide improved diagnostic accuracy when compared to antithyroglobulin antibodies in an effort to increase the certainty of the diagnosis. However, fine needle aspiration (FNA) and cytological testing continue to play a crucial role in making the diagnosis when Hashimoto's thyroiditis is clinically suspected but antibody titers are not raised [42,49–51]. The presence of Hurthle cells and the degree of lymphocytic infiltration have been found to be directly correlated with the severity of the disease when defining important cytological findings. Additionally, as the illness worsens, the thyroid gland colloid is destroyed, and the gaps between follicular cells get smaller, changing the microscopic appearance of FNA biopsy results. The extent of the affected tissue has been discovered to be exactly proportionate to the severity of the disease, providing more explanation of how microscopic appearance correlates with disease severity. The presence of many hyperplastic follicular cells may occasionally result in a false diagnosis of follicular cancer despite the diagnostic sensitivity and accuracy of cytological examination. On the other hand, if there are a lot of Hurthle cells present, some neoplasms, including Hurthle cell tumour, may be misinterpreted as Hashimoto's thyroiditis [52,53]. Another technique that is frequently used to identify thyroid problems is radioactive iodine uptake (RAIU). The use of RAIU in the Hashimoto's thyroiditis diagnosis has been controversial for a long time. An ultrasound can be used to detect thyroid pathology and may be a less intrusive study. The anatomical properties of the gland are revealed by ultrasonography, which also reveals any significant alterations to the gland. Ultrasonography can assist distinguish Hashimoto's thyroiditis in goitres with unclear causes, and it can also help determine the reason for functional impairment and the need for treatment [54,55]. An accurate diagnosis of the condition is frequently made using the thyroid glands morphological characteristics, serum TSH levels, serum antithyroid antiglobulin titers, radioactive iodine uptake of the gland, and reaction to the perchlorate discharge test. In fact, if at least two of the aforementioned tests confirm the diagnosis of Hashimoto's thyroiditis, the doctor can be pretty confident in their decision. IgG-4 thyroiditis and nonIgG-4 thyroiditis have been defined as subtypes of Hashimoto's thyroiditis in several recent investigations. This differential could be significant since non-IgG-4 thyroiditis shows relatively subtle

histological alterations while IgG-4 thyroiditis has been linked to severe lymphoplasmacytic infiltration, substantial fibrosis, and lymphoid follicle development [19,56].

#### **Treatment Options Available For Hashimoto's Thyroiditis**

##### **❖ Medical and Surgical treatments for HT**

Medication could be used to treat hyperthyroid conditions. The main strategy is to lower the hormone using medications that stabilize the hormone level. Depending on the scenario, treatment lasts typically between 1.5 and 2 years. As soon as the treatment begins, the dosage and thyroid hormone levels both steadily decrease towards stabilization. However, there have been instances where patients did not benefit from the treatment. Another, more extreme treatment option was radioactive iodine in such cases. Nevertheless, because it involved radiation, this treatment should only be used as a last resort. If a female patient is of childbearing age, it is better to hold off on the radioactive iodine therapy unless she is seriously ill. This is because the patient must put off any plans to have children until the radiation-iodine treatment is finished [57–59]. In addition, surgery may be used to treat hyperthyroid conditions by removing the sections of the gland that are swollen. Only when the thyroid functions were stabilized could he be carried out. Patients with hypothyroidism, as opposed to those with hyperthyroidism, would require continual treatment. The goal of hypothyroidism treatment is to replace the body's depleted thyroid hormone, and one natural method is to increase the patient's intake of salt and iodine [60,61]. While Hashimoto's thyroiditis and hypothyroidism patients receive treatment in the form of the synthetic thyroid hormone thyroxin, many still have hypothyroid symptoms while having normal thyroid hormone levels. Therefore, more research is necessary to thoroughly comprehend the mechanisms underlying hyperthyroidism in order to develop an effective medication that will not only treat the symptom of hypothyroidism but also completely eradicate its underlying cause. Although there is currently no medicine available for this illness, surgery may be an option should the goitre enlarge. Surgery should be the last resort, though, as patients will require synthetic thyroid hormone for the rest of their lives if the thyroid gland is removed [62–64].

##### **Gut healing**

Leaky gut, or gut dysbiosis, is thought to be the primary factor in the majority of thyroid disorders. In addition to making the intestines less effective at absorbing nutrients, a leaky gut also allows poisons and microorganisms that shouldn't be there to enter the body and cause an immunological reaction. The same factors that can cause a leaky gut in the first place, such as underlying food allergies, frequent use of antibiotics, certain medications, and lifestyle choices, can also cause yeast and/or bacterial overgrowths, which can disturb the lining of the gut and eventually result in autoimmune diseases [65–67]. In general, gut healing involves four steps: 1) eliminating any substances (such as cadmium (Cd), mercury (Hg), arsenic (As), lead (Pb), etc.) that are interfering with the digestive environment, 2) reintroducing healthy digestive enzymes into the digestive system, 3) reestablishing probiotic bacteria in the gut, and 4) repairing the gut lining. The gut can heal by avoiding inflammatory foods including gluten, wheat, dairy, eggs, nuts, and legumes. Foods can be reintroduced once the

digestive system is functioning correctly and is in good condition [68]. The digestive tracts health and function, the immune system's homeostasis, and host energy metabolism are all significantly influenced by the gut microbiome. Probiotics aid in the restoration of healthy gut microorganisms. Maintain a healthy environment for the body by limiting the growth of dangerous bacteria, preventing yeast overgrowth, promoting effective communication between the brain and the intestinal system, reducing inflammation, and more. Probiotics, especially *Lactobacillus* strains, improve the integrity of the intestinal barrier, which may prevent disease phenotypes like gastrointestinal infections, inflammatory bowel disease, and irritable bowel syndrome from occurring. It may also maintain immune tolerance by reducing bacterial translocation across the intestinal mucosa. Additionally, probiotics can change how immune cells and intestinal epithelia react to bacteria in the intestinal lumen as well as how they influence intestinal immunity [69–72].

#### ➤ **Foods That Interfere With The Digestive Process**

##### ▪ **Alcohol**

Patients with Hashimoto's disease and hypothyroidism are also becoming more intolerant to alcohol. This is due to the direct cellular toxicity that alcohol has on thyroid cells, which results in thyroid suppression and decreased thyroid volume. Additionally, chronically consuming large amounts of alcohol can block the production of the thyroid hormones T3 and T4 as well as lower type II 5'-deiodinase activity, which lowers free T3 levels and prolongs symptoms [73].

##### ▪ **Gluten**

Wheat, barley, rye, kamut, oats, quinoa, buckwheat, and millet all contain the protein known as gluten. Lectins, saponins, and protease inhibitors are all present in significant concentrations in gluten. When a patient with gluten sensitivity consumes gluten, the gluten will pass through the stomach and into the small intestine, forcing the body to manufacture the chemical zonulin, which weakens the intestinal walls and allows for the passage of particles and liquids. When this occurs, the body gradually develops chronic inflammation, making a person more prone to autoimmune disorders including thyroid disease and other dangerous illnesses. Additionally, because many of the tissues in our body are similar to gluten, when gluten enters the bloodstream as a result of a leaky gut, the body produces antibodies that attack both the gluten and our own tissues [66, 67].

##### ▪ **Eggs and dairy**

Enzymes found in egg whites are designed to safeguard the yolk during embryo development. Protein chains can be broken apart by these enzymes, rendering the smaller chains worthless. As lysozyme has the capacity to breach the gut barrier and latch on to other proteins and bacteria, it can do so, causing a leaky gut syndrome. On the other side, dairy products contain protease inhibitors that cause leaky gut and increase blood insulin levels since they are insulin-genic. Dairy products also contain A1 casein, which can lead to leaky gut syndrome, worsen thyroid gland inflammation, and eventually affect how well the thyroid gland functions [66, 68].

#### ❖ **Treating Hashimoto's thyroiditis with herbs**

##### ▪ **Guggul**

The plant *C. mukul*, popularly known as guggul, helps the thyroid function. *C. mukul*, a member of the *Burseraceae* family, is known for its aromatic gummy resins, which have a wide range of medical applications. Guggul or *Commiphora* is said to be beneficial for increasing the thyroid gland intake of iodine and for elevating thyroid peroxidase enzyme activity. The greater T3 produced along with a healthy change in the T3 to T4 ratio indicates a thyroid support effect. By promoting the basic metabolic function of the thyroid, guggul may also lower cholesterol levels. Guggul contains guggulsterones, which work on the bile acid receptor to metabolize lipids and also support the hypolipidemic effects of guggul [74–77]. The atherosclerosis-causing process of low-density lipoprotein (LDL) oxidation is inhibited by guggul. With the addition of Guggul, the amount of LDL can also be changed. Through the thyroid function, which has been demonstrated in animal studies, it may also reduce the total fat level [78].

##### ▪ **Iris Versicolor**

*I. Versicolor*, popularly known as blue flag, is a little wild iris found in North America's marshy regions. *I. Versicolor* also aids in the thyroid glands function by increasing T3 synthesis. It is a detoxifying agent that is specifically used to treat goitre and enlarged thyroid. Additionally, it is used to treat splenomegaly and hepatomegaly. Alkaloids, volatile oils, resins, and oleoresin iridin are all found in this plant. Since antiquity, this therapeutic plant has been applied topically, orally, or both. This specifically affects goitre and thyroid hypertrophy [78].

##### ▪ **Bladder wracks**

*Fucus vesiculosus*, a genus of brown algae that belongs to the *Fucaceae* family, is commonly found intertidally, particularly in the Pacific Ocean. The flavonoid *flucoxanthin* is found in *F. vesiculosus*, and *fucus* is said to have the highest antioxidant activity of any edible seaweed. Iodine is abundant in *fucus*, which also has a high bioavailability of iodine. Additionally, it contains a lot of minerals including calcium and potassium as well as a small quantity of phosphorus, selenium, magnesium, and zinc. Additionally, it is sufficiently rich in vitamins B2, B3, and B6, as well as A, D, E, and K. When ingested in the proper quantity, the vitamins and minerals included in *fucus* aid to improve thyroid function. *Fucus* blades that have been recently cut and dried in dim sunlight contain more iodine [79–81]. Additionally, it aids in lowering the blood's trans-sialidase activity, an enzyme that deals with cholesterol buildup. Due to the link between increased lipidemia and decreased metabolism, this may be beneficial for people with hypothyroidism. Iodine concentrations ranged from 16 µg/g in *nori* (*Porphyra tenera*) to 8165 µg/g in processed kelp granules derived from *Laminaria digitata* in the 12 species examined. The blood enzyme trans-sialidase, which is linked to the buildup of cholesterol, can also be reduced by *fucus*. Patients with low thyroid function may benefit from this since hyperlipidemia is linked to impaired metabolism [82].

## Conclusion and Future Direction

A general description of Hashimoto's thyroiditis, including its causes, risk factors, epidemiology, pathophysiology, and combination therapy, including surgical, nonsurgical, and herbal alternatives, is provided in the first section of our review articles. Our research reveals that while non-pharmacological and natural supplements produce reasonable results but take some time to act and have no negative side effects, medication does offer some relief but does not, Completely heal the body. To comprehend how to treat Hashimoto's thyroiditis better, more randomised controlled research is required. We hope to conduct more study on Hashimoto's thyroiditis in the future. Future study involving counselling will be carried out in our country or state with the aid of our colleagues in order to assess patients' physical and mental health and provide more precise data on Hashimoto's thyroiditis and its improved therapy.

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## Conflict of Interest

The authors confirm that they have no known financial or personal conflicts of interest that would affect the research presented in this study.

## Informed Consent

Using review articles, websites, and other sources for research content.

## Ethical Statement

Don't evaluate each day by the harvest you bring in, but rather by the seeds you sow instead.

## Author Contribution

Equitable contribution

**Table.1: Current status of clinical trials on Thyroid diseases.**

| Drug                                             | Mode of administration | Disease | Enrollment | Allocation/Intervention model/Masking                                              | Official Title of the study                                                                                                                        | Status  | Clinical trial | Year |
|--------------------------------------------------|------------------------|---------|------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------|------|
| Gasless BABA/ Classic BABA                       | Interventional         | Thyroid | 28         | Randomized/ Parallel Assignment/ Triple (ParticipantInvestigatorOutcomes Assessor) | A Prospective, Randomized, and Controlled Study of the Safety and Efficacy in Gasless BABA(Bilateral Axillo-breast Approach) Robotic Thyroidectomy | NA      | NCT03922282    | 2019 |
| determination of thyroid hormones and antibodies | Observational          | Thyroid | 50         | NA                                                                                 | Association of Oral Lichen Planus and Thyroid Disease                                                                                              | NA      | NCT04523077    | 2020 |
| Dexamethasone/ NaCl 0.9%                         | Interventional         | Thyroid | 152        | Randomized/ Parallel Assignment/Double (ParticipantInvestigator)                   | Preoperative Single-dose Steroid Application for the Treatment of Nausea and Vomiting After Thyroid Surgery                                        | Phase-3 | NCT01189292    | 2015 |
| Tums/ Calcitriol                                 | Interventional         | Thyroid | 82         | Randomized/ Parallel Assignment/ None (Open Label)                                 | Does Preoperative Calcium and Calcitriol Decrease Rates of Post                                                                                    | NA      | NCT03869398    | 2019 |

|                                                   |                |         |      |                                                                                                  |                                                                                                                                                |         |             |      |
|---------------------------------------------------|----------------|---------|------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------|------|
|                                                   |                |         |      |                                                                                                  | Thyroidectomy Hypocalcemia.                                                                                                                    |         |             |      |
| FNB/ Core biopsy                                  | Interventional | Thyroid | 60   | Randomized/ Parallel Assignment/ Single (Participant)                                            | Effectiveness of Core-Needle US Guided Biopsy as Primary Tool For Diagnosis of Thyroid Nodules, A Prospective Study                            | NA      | NCT04759053 | 2021 |
| Non-narcotic group regimen/Narcotic group regimen | Interventional | Thyroid | 126  | Randomized/ Parallel Assignment/None (Open Label)                                                | Are Narcotic Pain Medications Necessary Following Thyroidectomy and Parathyroidectomy                                                          | Phase-1 | NCT03640247 | 2019 |
| PIPC piperacillin sodium/ CEZ, cefazolin sodium   | Interventional | Thyroid | 2164 | Randomized/ Parallel Assignment/Quadruple (ParticipantCareProviderInvestigatorOutcomes Assessor) | Antimicrobial Prophylaxis for the Prevention of Surgical Site Infection in Thyroid and Parathyroid Surgery                                     | NA      | NCT01805856 | 2013 |
| thyroidectomy                                     | Interventional | Thyroid | 122  | Randomized/ Parallel Assignment/Quadruple (ParticipantCareProviderInvestigatorOutcomes Assessor) | Transection of Sternothyroid Muscle Increases the Rate of Exposure of the External Branch of the Superior Laryngeal Nerve During Thyroidectomy | NA      | NCT05421559 | 2022 |
| TRH (Thyrotropin Releasing Hormone)               | Interventional | Thyroid | 96   | N/A/ Single Group Assignment/None (Open Label)                                                   | Study of Thyrotropin Releasing Hormone in Patients With Thyroid or Pituitary Abnormalities                                                     | Phase-2 | NCT00054756 | 2018 |
| thyroid function tests                            | Observational  | Thyroid | 62   | NA                                                                                               | Ectopic Pregnancy and Thyroid Disorders                                                                                                        | NA      | NCT05446012 | 2022 |
| NA                                                | Observational  | Thyroid | 05   | NA                                                                                               | Early Detection of Autoimmune Thyroid Heart Disease Via Urinary Exosomal Proteins.                                                             | NA      | NCT03984006 | 2021 |
| NA                                                | Observational  | Thyroid | 2498 | Ecologic or Community                                                                            | Thyroid Disorders in Malaysian: A Nationwide Multicentre Study                                                                                 | NA      | NCT02190214 | 2016 |
| NA                                                | Observational  | Thyroid | 253  | Other                                                                                            | Thyroid Disease in Pregnancy and Its Impact on the Quality of Life                                                                             | NA      | NCT04167423 | 2022 |
| NA                                                | Observational  | Thyroid | 50   | Cohort                                                                                           | The Role of an Optical Probe in the Detection of Thyroid Cancer                                                                                | NA      | NCT01792492 | 2016 |

|                                   |                |         |       |                                                                |                                                                                                                                          |    |             |      |
|-----------------------------------|----------------|---------|-------|----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|----|-------------|------|
|                                   |                |         |       |                                                                | and Normal Thyroid Tissue in a Thyroidectomy Specimen: A Pilot Study                                                                     |    |             |      |
| NA                                | Observational  | Thyroid | 23143 | Cohort                                                         | Scientific Protocol for the Study of Thyroid Cancer and Other Thyroid Diseases in Ukraine Following the Chernobyl Accident               | NA | NCT00341094 | 2020 |
| Elastography                      | Interventional | Thyroid | 188   | N/A /Single Group Assignment/ None (Open Label)                | The Role of Elastography in the Diagnosis of Thyroid Nodules                                                                             | NA | NCT01292044 | 2015 |
| NA                                | Observational  | Thyroid | 220   | NA                                                             | Mohawk Culture, Behavior, Toxicant Exposure and Health                                                                                   | NA | NCT00043238 | 2015 |
| NA                                | Observational  | Thyroid | 30    | Case-Control                                                   | A Phase I Study of <sup>99m</sup> Tc Pertechnetate Produced in High Energy Cyclotron (CYCLOTEC) in Patients With Thyroid Scan Indication | NA | NCT02307175 | 2017 |
| NA                                | Observational  | Thyroid | 117   | NA                                                             | Study to Improve Thyroid Doses From Fallout Exposure in Kazakhstan                                                                       | NA | NCT00480428 | 2019 |
| NA                                | Observational  | Thyroid | 19456 | Cohort                                                         | Scientific Protocol for the Study of Thyroid Cancer and Other Thyroid Disease in Belarus Following the Chernobyl Accident                | NA | NCT00339716 | 2020 |
| Decision Aid                      | Interventional | Thyroid | 93    | Randomized/Parallel Assignment/None (Open Label)               | Shared Decision Making in Graves Disease - Graves Disease (GD) Choice                                                                    | NA | NCT02107794 | 2015 |
| NA                                | Observational  | Thyroid | 77    | Cohort                                                         | NeoThyr - the Role of Mitochondrial dysfunction in Newborns of Mothers With Autoimmune Thyroid Disease                                   | NA | NCT02061111 | 2023 |
| Dexamethasone/<br>natriumchloride | Interventional | Thyroid | 120   | Randomized/ Parallel Assignment/<br>Triple (ParticipantCarePro | Nausea and Pain Prophylaxis During Thyroid Surg                                                                                          | NA | NCT00569920 | 2009 |

|                                                                       |                    |             |      |                                                                         |                                                                                                                                                                                                |    |                     |      |
|-----------------------------------------------------------------------|--------------------|-------------|------|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|---------------------|------|
| de 0,9%/<br>dexamethason<br>e                                         |                    |             |      | viderInvestigator)                                                      | ery, a Comparison of<br>Low-Dose and High-<br>Dose<br>Dexamethasone to<br>Placebo                                                                                                              |    |                     |      |
| thyroid USG<br>was perform,<br>blood samples                          | Observation<br>al  | Thy<br>roid | 160  | Case-Control                                                            | The Frequency<br>of Thyroid Diseases<br>in Women With<br>Breast Cancer                                                                                                                         | NA | NCT04<br>40677<br>9 | 2020 |
| Thyroidectom<br>y/Bupivacaine<br>/ Saline<br>Solution                 | Interventio<br>nal | Thy<br>roid | 91   | Randomized/ Parallel<br>Assignment/Double (Partic<br>ipantInvestigator) | Bupivacaine<br>Application Reduces<br>Postthyroidectomy<br>Pain: Cerrahpaşa<br>Experience                                                                                                      | NA | NCT02<br>98109<br>5 | 2016 |
| no<br>intervention                                                    | Observation<br>al  | Thy<br>roid | 260  | Ecologic or Community                                                   | Association<br>Between Thyroid Fu<br>nction and Diabetes<br>Complications in<br>Elderly Patients<br>With Type 2<br>Diabetes Mellitus in<br>China                                               | NA | NCT03<br>00133<br>6 | 2016 |
| Levothyroxine<br>,<br>Propylthioura<br>cile                           | Interventio<br>nal | Thy<br>roid | 4657 | Randomized/ Parallel<br>Assignment/Double (Partic<br>ipantInvestigator) | Impact of<br>Treating Thyroid Ho<br>rmon Dysfunction<br>During Pregnancy: A<br>Randomized<br>Controlled Trial of<br>Universal Screening<br>Versus Case Finding                                 | NA | NCT00<br>84675<br>5 | 2011 |
| NA                                                                    | Observation<br>al  | Thy<br>roid | 80   | Case-Control                                                            | Harmonic FOCUS<br>Versus<br>Conventional<br>Technique in Total<br>Thyroidectomy for<br>Benign Thyroid Dise<br>ase -A Prospective,<br>Comparative,<br>Multicenter,<br>Observational Study       | NA | NCT00<br>66631<br>5 | 2008 |
| SPRESS<br>MEDICA S.r.l.<br>Via Buccari<br>16153 Genova<br>(GE), Italy | Observation<br>al  | Thy<br>roid | 20   | Cohort                                                                  | Comparison of<br>Different Types of<br>Electrostimulation<br>Probes for<br>Intraoperative<br>Nerve Monitoring<br>During<br>Thyroidectomy                                                       | NA | NCT03<br>46091<br>2 | 2018 |
| NA                                                                    | Observation<br>al  | Thy<br>roid | 86   | NA                                                                      | Pharmacogenomic<br>Response to<br>Thyrotropin-<br>Releasing Hormone<br>Stimulation in<br>Healthy<br>Volunteers:The<br>Influence of a<br>Common Type 2<br>Deiodinase Genetic<br>Polymorphism on | NA | NCT00<br>81214<br>9 | 2017 |

|                                                                                 |                |         |      |                                                                                 |                                                                                                                                                                    |         |             |      |
|---------------------------------------------------------------------------------|----------------|---------|------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------|------|
|                                                                                 |                |         |      |                                                                                 | Serum T3                                                                                                                                                           |         |             |      |
| Liothyronine and Levothyroxine                                                  | Interventional | Thyroid | 18   | Randomized/Crossover Assignment/Triple (Participant/Care Provider/Investigator) | Peripheral Thyroid Hormone Conversion and Glucose and Energy Metabolism                                                                                            | Phase-2 | NCT00106119 | 2015 |
| Harmonic Scalpel (Ethicon Endo-Surgery, USA)/Ligasure Small Jaw (Covidien, USA) | Interventional | Thyroid | 100  | Randomized/ Parallel Assignment/Double (Participant/Outcomes Assessor)          | Randomized Controlled Trial Comparing the Utility of an Ultrasonic Coagulating Device (UCSD) With Electrothermal Bipolar Vessel Sealer (EBVS) in Thyroid Surgery.  | NA      | NCT01765686 | 2017 |
| NA                                                                              | Observational  | Thyroid | 1200 | NA                                                                              | Development and Validation of a Thyroid-Specific Quality of Life Measure                                                                                           | NA      | NCT00150033 | 2008 |
| Radioiodine                                                                     | Observational  | Thyroid | 12   | Case-Control                                                                    | Use of Low-dose Radioiodine for Ablation of Thyroid Remnants in Patients With Graves' Disease Following Thyroidectomy                                              | NA      | NCT03110835 | 2017 |
| endoscopic thyroidectomy                                                        | Observational  | Thyroid | 300  | Cohort                                                                          | A Novel Technique for Endoscopic Transaxillary Thyroidectomy: a Preliminary Report and Comparison With the Open Procedure                                          | NA      | NCT05735054 | 2023 |
| serum sampling                                                                  | Observational  | Thyroid | 96   | Cohort                                                                          | Antithyroidale Antikörper Mit Oder Ohne Subklinische Hypothyreose Bei Weiblicher Infertilität in Der Schwangerschaft Und im Wochenbett.                            | NA      | NCT04249271 | 2020 |
| Hyalobarrier/ Guardix-SG                                                        | Interventional | Thyroid | 198  | Randomized/Parallel Assignment/Double (Participant Outcomes Assessor)           | Prospective, Randomized, Double Blind, Multicenter Study for Hyalobarrier® to Evaluate Anti-adhesive Effect and Safety Compared to Guardix-SG® After Thyroidectomy | Phase-3 | NCT01696305 | 2014 |
| NIRF imaging in thyroid                                                         | Interventional | Thyroid | 30   | N/A /Single Group Assignment/ None (Open                                        | The Use of Near-Infrared Fluorescence                                                                                                                              | NA      | NCT03012438 | 2018 |

|                                                        |                |         |      |                                                                        |                                                                                                                                                                         |         |             |      |
|--------------------------------------------------------|----------------|---------|------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------|------|
| surgery                                                |                |         |      | Label)                                                                 | Imaging in Parathyroid Visualization During Thyroid Surgery: a Pilot Study                                                                                              |         |             |      |
| Transoral endoscopic thyroidectomy vestibular approach | Interventional | Thyroid | 10   | N/A/ Single Group Assignment/None (Open Label)                         | A Prospective Evaluation of the Feasibility and Safety of the Transoral Endoscopic Thyroidectomy Vestibular Approach (TOETVA) as a Treatment for Benign Thyroid Nodules | NA      | NCT03158961 | 2021 |
| platysma suture/ no platysma suture                    | Interventional | Thyroid | 80   | Randomized/ Parallel Assignment/Double (Participant Outcomes Assessor) | Platysma Trial - a Randomized Controlled Trial of Platysma Suturing Versus no Sutures for Wound Closure After Primary Thyroid Surgery                                   | NA      | NCT02951000 | 2017 |
| Thyroid surgery                                        | Observational  | Thyroid | 3500 | Cohort                                                                 | Influence of Factors Specific to Patient, Procedure or Surgeon on Thyroid Surgery Outcomes                                                                              | NA      | NCT02813733 | 2016 |
| Thyroidectomy                                          | Observational  | Thyroid | 3800 | Case-Control                                                           | The Impact of COVID-19 Pandemic on Thyroid Surgery in Italy: Results From a Nation-wide Multicentric Study                                                              | NA      | NCT04635813 | 2020 |
| Prednisone                                             | Interventional | Thyroid | 30   | Randomized /Parallel Assignment/ None (Open Label)                     | Randomized Controlled Trial of Preoperative Steroids in Autoimmune Thyroid Disease                                                                                      | Phase-4 | NCT04542278 | 2022 |
| NA                                                     | Observational  | Thyroid | 1000 | NA                                                                     | Thyroid Disease Serum Repository                                                                                                                                        | NA      | NCT00592605 | 2017 |
| NA                                                     | Observational  | Thyroid | 60   | Case-Control                                                           | Can Thyroid Levels Affect Topographic, Densitometric and Aberrometric Values of the Cornea                                                                              | NA      | NCT04752969 | 2021 |
| Toetva                                                 | Observational  | Thyroid | 18   | Case-Only                                                              | Feasibility and Complications After Transoral Endoscopic Thyroidectomy Via Vestibular Approach (TOETVA) - a                                                             | NA      | NCT05396703 | 2023 |

|             |                |         |    |                                               |                                                                                                                                                                            |         |             |      |
|-------------|----------------|---------|----|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------|------|
|             |                |         |    |                                               | Single-Center First Experience Case Series and Systematic Review                                                                                                           |         |             |      |
| CTC/ G-PERT | Interventional | Thyroid | 25 | N/A/Single Group Assignment/None (Open Label) | A Pivotal Phase III Study of Cyclotron-produced Tc-99m Pertechnetate (CTC) Compared to Generator-produced Tc-99m Pertechnetate (G-PERT) in Subjects With Thyroid Disorders | Phase-3 | NCT02980679 | 2022 |

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