THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2022.56514
Med Bull Sisli Etfal Hosp 2022;56(1):21–40

Review

Non-Toxic Multinodular Goiter: From Etiopathogenesis to Treatment

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Abstract

Goiter term is generally used for defining the enlargement of thyroid gland. Thyroid nodules are very common and some of these nodules may harbor malignancy. Multinodular goiter (MNG) disease without thyroid dysfunction is defined as non-toxic MNG.

There are many factors in etiology for development of MNG. They can be classified as iodine dependent and non-iodine dependent factors basically. Beyond this basic classification, the effect of many environmental and acquired factors is also effective on the development of goiter.

Many methods have described for diagnosis and treatment for non-toxic MNG. Biochemical tests, imagining methods, invasive and non-invasive methods have been used for diagnosis for many years. Each method has advantages and disadvantages, separately. Although the best method for diagnosis is still debatable, distinguishing malignant nodules from benign nodules is the first and most important step for MNG.

Biochemical tests such as serum thyroid stimulating hormone (TSH) measurement, thyroid hormone measurement; and thyroid ultrasonography are used for diagnosis of MNG, traditionally. Nowadays, there are some new techniques were developed like ultrasound-elastography. Furthermore, thyroid scintigraphy may be used if there is abnormal TSH measurement. Fine-needle aspiration biopsy and some cross-sectional imaging methods (computed tomography, magnetic resonance imaging, and positron emission tomography) could be used, too.

After a certain diagnosis is made, treatment options should be evaluated. Many treatment methods have been used for goiter from ancient times upon today. From non-invasive methods such as medical follow-up to invasive methods such as lobectomy or thyroidectomy are options for treatment. Patients with compression symptoms due to an enlarged thyroid gland are usually candidates for surgery. In this study, it is aimed to determine the most appropriate treatment for the patient by discussing the advantages and disadvantages of all these methods.

The present review discusses definition of goiter term, etiology, epidemiology, pathogenesis, diagnostic methods, and treatment methods for nontoxic MNG.

Keywords: Etiology, non-toxic multinodular goiter, pathogenesis, treatment

Please cite this article as "Unlu MT, Kostek M, Aygun N, İsgor A, Uludag M. Non-Toxic Multinodular Goiter: From Etiopathogenesis to Treatment. Med Bull Sisli Etfal Hosp 2022;56(1):21–40".

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Submitted Date: February 19, 2022 **Accepted Date:** March 27, 2022 **Available Online Date:** March 28, 2022

Thyroid diseases are one of the most common endocrinopathologies and resulting from functional and structural changes in the thyroid tissue. These can range minor structural changes that do not affect patient's health quality, to major functional and structural changes that could affect health quality seriously. Goiter is the most common one among these diseases.[1]

Goiter is a clinical term derived from Latin word "guttur" which can be translated into English as "throat," meaning an enlargement of thyroid gland.[2] Goiter was described from early ancient times (B.C. 1500) in China and has come up to today. In ancient times, burnt seaweed was tried in the treatment of patients with goiter, and it is probably not known to be rich in iodine content, this treatment method was applied by trial. Roman legions met endemic goiter disease in Alpine villages when they were marching to conquer Celt lands. From that time to today, there is a famous adage that "Who wonders at a swollen neck in the Alps." (Quis tumidum guttur miratur in Alpibus). Also depiction of patients with goiter is common among Renassience frescoes. In a famous frescoe by Michelangelo exhibited in the Sistine Chapel, the God is depicted with goiter. However, some authors claim that Michelangelo portrayed himself as a self-portrait in that frescoe.[3]

The etiology of goiter is multifactorial; genetical; and environmental. Although there is a huge effect by genetical and familial disorders, iodine deficiency is the major factor in young school children, young adults, and elderly people for goiter. Goiter is common in almost every country. Serious iodine deficiency causes symptoms by hypothyroidism in a wide range from minor to major diseases. Goiter should be considered as a serious public health problem because of these reasons.[1]

Goiter may be diffuse or nodular as morphological.[4] Goiter starts as diffuse form generally and renders nodular form with some several factors affect.[2]

Surgical treatment is one of the most frequent options for Multinodular Goiter. In these patients, the most common indications for surgery are; malignancy, substernal goiter, suspicion of malignancy, and hyperthyroidism that resistant to medical treatments.[5]

There are many surgical procedures for the treatment of multinodular goiter (MNG) from past years to the present. The size and location of nodul, cytological results are important factors in choosing the best surgical procedure for MNG.

In the present review, we discuss about clinical features and treatment strategies of Multinodular Goiter disease.

Definitons

There are many different definitions about goiter in the literature, according to the different study types. In the early 20th centuries, according to the autopsy series, goiter was defined as enlargement of thyroid gland more than 30–35 gram (g).[1] Later, necessity of definition for goiter in alive people was realized. Thus, a new definition of goiter was developed. According to that, goiter was defined as "each of the lateral lobes of thyroid gland is larger than the terminal phalanges of the thumb of the person examined."[6] An another definition of goiter is an enlargement of thyroid gland 2 times or more of the normal size.[7] However, the reliability of thyroid palpation is worse in smaller growths. Therefore, since the use of thyroid ultrasonography (USG) became widespread, the sonographic thyroid volume has been used as a definition of goiter.[1]

In studies, usually goiter is defined as an enlargement of the thyroid volume more than 2 standard deviation compared to the normal thyroid volume without nodule on thyroid USG, family history, antithyroid antibodies, and iodine deficiency.[8–12]

On the other hand, there are different studies which describe goiter as enlargement on thyroid gland more than 3 standard deviation on people without iodine deficiency.[13]

Even though there are some differences in studies according to the region, goiter is defined as approximately over 18–19 milliliter (mL) on women and over 25 mL on men.[9–13]

Goiter can be classified as diffuse or nodular due to its morphological features. If the thyroid gland enlarge diffusely, it is named diffuse goiter. If there are one or more nodules in thyroid, which were transformed with different shape and/or function compared to the normal gland, it is defined as nodular goiter.[4]

Nodular goiter is defined as solitary thyroid nodul, if the enlargement is derived from a single nodul. When there are more than one nodul, it is defined as Multinodular Goiter.[14]

Instead of the terms "solitary thyroid nodule" and "MNG," Knobel suggested using the more descriptive and accurate term "nodular thyroid disease" to describe single and multiple palpable or non-palpable nodules.[2]

Goiter can also be classified sporadic and endemic as epidemiologically. It is named sporadic if the prevalence of goiter <10% in a region, endemic if it is more than 10%.[2]

Nodular goiter can be classified toxic or non-toxic based on its functionality. Non-toxic goiter is usually euthyroid but in some patients it may be associated with hypothyroidism.[7]

Toxic nodular goiter may develop from a solitary nodule or in a MNG when one or more of the nodules are hyperfunctional.[7]

Solitary thyroid nodules are more uniform in terms of pathological, clinical and molecular features. However, there

may be hyperfunctional, hypofunctional or normal nodules in multinodular goiter.[2]

It is defined as simple nodular goiter, in the absence of thyroiditis, autoimmune thyroid disease and thyroid function disorder.[4] On the other hand, non-toxic diffuse goiter is described as a diffuse enlargement of thyroid gland independent from thyroid-stimulating hormone (TSH).

Epidemiology

Goiter effects approximately more than one tenth of the world population less or more.[1] However, goiter incidence varies wide range due to the affects of region, climate, genetic factors, iodine deficiency or sufficiency and other environmental factors. According to the study of Tunbridge et al.,[15] with 2947 patients; the incidence of MNG in Northern England, where there is no iodine deficiency, was determined as 5.9%. The male/female ratio was determined 1/13. Moreover, multinodular goiter ratio was found significantly higher in female patients over the age of 45.

It is determined that the incidence of multinodular goiter in the elderly population may increase up to 10% in regions where iodine deficiency is subsequently solved.[16]

It is seen that there are some changes in the prevalence of goiter with the developments in technology and imaging methods from the past to the present. The nodule prevalence detected by USG; varies in a wide range from 19% to 67%.[17] This wide range is derived and effected by the factors such as the experience of physician and sensitivity of USG device. Only 4–7% of the nodules detected with USG can be noticeable by palpation.[17]

Although, diseases such as nodular goiter, diffuse goiter are considered to be more frequent in female patients; some authors advocate that there is no affect of sex in these diseases.[18,19]

The type of nodularity changes with getting older. It is seen usually as a single nodule between the age of 20 and 40, but over the age of 40, especially over the age of 60, multinodular goiter is more common.[1]

Etiology

Although it is known that the etiology of goiter is multifactorial; still main subject for prevention of goiter is providing sufficient amounts of iodine in the diet.[20]

Etiological factors for goiter are listed below;

1) Iodine
2) Non-iodine factors
    a. Genetical Factors
    b. Environmental Pollutants
        i. Iodine uptake inhibitors
            1. Perchlorat
            2. Thiocyanate
            3. Nitrate
        ii. Compounds effecting thyroid hormone receptor directly
            1. Polychlorinate biphenyl (PCB)
            2. Polybrominate diphenylester (PBDE)
            3. Bisphenol-A
            4. Triclosan
        iii. Compounds that inhibit T4 from binding to the thyroid-binding protein transthyretin
            1. PBDE
            2. Hydroxylated PCB
        iv. Compounds that inhibit TPO activity
            1. Isoflavones
        v. Compounds that reduce T4 half-life by inducing liver enzymes
            1. Organochlorine pesticides
            2. Dioxins and furans
        vi. Other compounds
            1. Strains
            2. Sunscreens
            3. Lead
    c. The other non-iodine factors
        i. Selenium
        ii. Cigarette smoke
        iii. Goitrogens
        iv. Sex
        v. Alcohol
        vi. Medical drugs
        vii. Insulin resistance
        viii. Socio-economic level

In this section some of these factors are examined.

Iodine

Iodine has a critical role in thyroid hormones synthesis. With the iodination of salts programs iodine deficiency rates has decreased but still iodine deficiency is a common public health issue in the world. Iodine deficiency affects population health in many different ways and these situations described as iodine deficiency related diseases. Iodine deficiency causes goiter in adults also problems in development of central nervous system in fetal and neonatal period.[21]

Iodine deficiency is described as a major responsible factor for developing structural and functional disorders of thyroid gland, in many epidemiological studies.[22]

The prevalence of goiter has an important role to determine iodine deficient regions.[23] Also there are many studies that describe a negative correlation between thyroid volume and iodine uptake in the literature.[24,25]

In Lithuania, which is considered an iodine-deficient region, significant differences were found in the prevalence of goiter and thyroid volumes after iodine prophylaxis started in 2005, and these results show the effects of iodine on the prevalence of goiter and thyroid volume.[26] In iodine-deficient regions such as Lithuania and Denmark, iodine prophylaxis can be considered a challenge, especially against endemic goiter. Thyroid gland enlargement is observed in 15.0% and 22.6% of the population, respectively, when viewed with USG in the regions of Denmark with moderate and severe iodine deficiency. In addition, palpable thyroid nodules were clinically detected in 9.8% and 14.6% of the population, respectively.[27]

Iodine deficiency is the most important factor for developing multinodular goiter in endemic goiter regions. However, there are some conflicts about iodine deficiency effect on sporadic goiter. It is considered as iodine deficiency makes it easier to development of goiter and prepares first step for multinodular goiter in individuals with genetic predisposition.[28]

The major cause of iodine deficiency is low dietary iodine intake because of iodine-poor ground. Although, iodine deficiency is usually seen in high altitude regions, altitude is not cause of that. Major factor of iodine deficiency is iodine shifting from soil to the seas due to heavy rains, snow, and the melting of ancient glaciers. Iodine deficiency can be balanced with the iodine obtained from sea water especially on sea coasts.[29-31]

When the prevalence of goiter was seen to have limited benefits in determining the prevalence of iodine deficiency, new methods were started. Urinary iodine excretion is one of the most commonly used methods today. Urinary iodine excretion in school age children is commonly used for determining iodine deficient areas. Due to school-age children's openness to the effect of iodine and its easily follow-up, this method is being used frequently today. Iodine deficiency is considered as a public health issue in regions urinary iodine excretion is over 100 µg/L or the prevalence of goiter is over 5%.[28]

On the other hand, high iodine uptake is also associated with an increased prevalence of goiter.[1]

Genetic Factors

The effect of genetic factors on endemic or sporadic goiter etiology has been known for long time. There is no single gene can be blamed for development of goiter because the disease is polygenic. Especially in studies obtained from monozygotic and dizygotic twins, it was found that genetic factors play a role in the development of goiter with no suspicion. The risk of goiter is increases 5–10 times in people with a first degree relative with goiter compared to control group.[20]

Thyroglobulin gene, thyroid-stimulant hormone receptor gene, the polymorphisms of Na+/I– symporter gene, and MNG marker located on chromosome 14 are considered responsible for genetical transmission, in particularly. If these genes are impaired, thyroid hormone synthesis decreases and thyroid volume increases as a compensatory response to this situation. This situation is known as compensatory goiter or also known as dishormonogenesis. It can be occurred in the early or late stages of life due to the degree of hormone deficiency.[20]

Non-iodine Factors

Environmental pollutants

The factors on goiter development, except iodine and genetic factors, have been investigated for long time. In many studies, environmental factors, medical drugs, gender, and some medical diseases are considered as responsible for development of goiter. Many substances that are frequently used in industry, home life and business life have a goitrogenic effect and affecting the thyroid gland. The effects of some of these substances have been proven, and some have not.[32]

Selenium

Selenium is an important cofactor for thyroid hormone synthesis, elimination and deiodination. Furthermore, it is an important component of glutathione compounds. Selenium has a significant effect on thyroid diseases, especially in autoimmune diseases.

There is some serious evidences about the effect of selenium on development of goiter even though it is not effective as iodine deficiency. In the literature, there are some conflicts about the effects of selenium on goiter, but in generally it is considered to be effective on development of goiter. Selenium deficiency may affect development of goiter for some degree if it is combined with iodine deficiency.[20]

Cigarette smoke

Using cigarette is one of most important modifiable risk factor for the development of nodular gaiter, except iodine.

There are too many studies about the effect of using cigarette on the development of gaiter. Furthermore, in the literature, there are some studies, showing that using cigarette has an effect for higher goiter prevalence in the iodine deficient areas, but not in iodine sufficient regions. In a study by Aydın et al.,[33] it is determined that using cigarette has an effect on goiter prevalence in iodine deficient regions of Turkey. On the other hand, Karatoprak et al.[34] showed that using cigarette has no significant effect on goiter prevalence in iodine sufficient region İstanbul in their study.

Especially, thiocyanate from the metabolism of cyanide in tobacco smoke is thought responsible for effects of using cigarette on development of goiter.[20]

Although there are many studies on the effect of smoking on the development of goiter in areas with iodine deficiency; there are not many studies investigating the effect of smoking alone. In addition, the effect of smoking on the prevalence of goiter could not be determined precisely because factors such as the amount and style of smoking depend on the person.[27,35]

There is a need for more studies about the specific effect of using cigarette on the development of goiter for more precise results.

Goitrogens

The first clue about this subject was determining the goitrogenic effect of cabbage. Like using cigarette; especially in iodine deficient regions, goitrogens with dietary uptake has thiocyanate and may be responsible for development of goiter.[29]

As a goitrogen; thiocyanate can be up taken in diet by vegetables such as cabbage, cauliflower, kale, broccoli, radish, rapeseed, lima beans, linseed, sorghum, sweet potato, and cassava.[36,37]

Also soybean, millet, babassu coconut, and cassava grass contain flavonoids that reduce the activity of thyroperoxidase.[37,38]

Gender

Debates are still ongoing about the reasons for the higher rates of sporadic MNG in females. The low prevalence of goiter and less enlargement of thyroid gland in postmenopausal women is thought to be due to genetic factors and sex hormones. Still there is no certain evidence about the relationship between X chromosome inactivation and goiter.[20]

Alcohol

Although the relationship between alcohol and goiter prevalence is unproven, there are some studies demonstrating alcohol can be etiological factor for goiter.[20]

In a study conducted in a large population in Denmark; it has been demonstrated that the risk of developing goiter can be reduced with the dose-response relationship in alcohol users.[39]

Medical drugs

Many drugs were considered responsible for developing MNG by their effect on iodine metabolism, induced TSH synthesis related hypothyroidism and estrogen metabolism. Using lithium for long time, in particularly, may cause hypothyroidism and as a result goiter. Iodine-containing drugs such as amiodarone, tolbutamide, and aminoglutethimide are well known examples.[40] Especially the use of oral contraceptives with high estrogen content is thought to have an effect on thyroid diseases.[20]

Insulin resistance

There are studies in the literature showing that insulin resistance causes enlargement of the thyroid gland. In the study conducted by Rezzonico et al.,[41] thyroid nodules were observed at a rate of 53% in patients with insulin resistance independent of obesity, and this rate was found as 19% in patients without insulin resistance. Also in the other study of Rezzónico et al.,[42] in the patients have been treated with metformin treatment for insulin resistance, it is demonstrated that thyroid volume decreased without thyroid hormone treatment.

Socio-economical level

In the literature, in Germany and Denmark; there are some studies about the relationship between goiter prevalence and socio-economic level. Especially, in the regions with lower socio-economic and educational level; it was determined that goiter prevalence was higher.[43,44]

Pathogenesis

The term of goiter is generally used for an enlargement of the thyroid gland through the compensatory response of follicular cells to a deficiency in hormone synthesis. However, there are studies demonstrating that this definition is not sufficient. For example, although iodine deficiency is known as the biggest cause of goiter (especially endemic goiter), the absence of goiter in the entire population in iodine-deficient regions or the presence of goiter in regions without iodine deficiency suggest that also there are some genetic and environmental factors, too.[37]

Nodular goiter is caused by hyperplasia of follicular cells in one or more areas of the thyroid gland. The basic goitrogenic process is the development of new follicular cells with abnormal growth potential that form new follicles or the increase in size of newly formed follicles. TSH is the most

important stimulator of growth and thyroid function under in vivo physiological conditions. Genetic, endogenous, and environmental factors can increase growth and affect over this basic process.[2] The thyroid tries to maintain a constant iodine concentration by increasing plasma inorganic iodine clearance in chronic iodine deficiency. Absolute iodine uptake tends to be lower in iodine-deficient areas even though increased clearance. Due to the continuous morphological deterioration of the thyroid, the adaptation process decreases over time and progresses from diffuse to multinodular hyperplasia when the goiter loses its adaptive efficiency.[45]

Derwahl and Struder claimed in their study that low iodine concentration in patients with goiter is a result, not a cause, for goiterogenesis. In their study, these two authors described a set of characteristic nodule features suggesting that the main cause of goiterogenesis is iodine-independent and cannot be simplified as the thought that nodular goiter develops solely as a result of iodine deficiency.[46]

During the thyroid hormone synthesis, iodine and H_2O_2 act as cosubstrates and if there are changes in concentration of iodine, it can affect H_2O_2 concentration. Furthermore, TSH can stimulate the generation of H_2O_2. H_2O_2 can be source for free radicals that make corruption in normal cells.[38]

Thyrocytes are important component of defense mechanism against free radicals in antioxidant enzymes such as glutathione peroxidase. If this antioxidative defense mechanism is ineffective, damage to thyrocytes proteins, lipids and DNA may occur.[47]

Low iodine levels and increased thyroid functions induces H_2O_2 activation which can result in DNA damage and somatic mutations.[38]

With hyperplasia caused by the decrease in iodine, there is a significant increase in the number of thyroid cells, accompanied by an increase in functional activity.

Due to the negative effect of the high replication rate in the thyroid gland on DNA repair, the mutagenic load of the thyroid gland is higher than other organs. Mutations that provide a growth advantage especially in the gene encoding TSH receptor or Gsα protein, are considered the most likely focal growth initiators.[48] Somatic mutations leading to activation of TSH receptors are found in approximately 60% of autonomously functioning nodules.[2] In the thyroid gland, thyrocytes responses are heterogeneous to these mutations. Thus, thyrocytes with mutations that will cause growth lead to focal growth areas. For this reason, many goiters become nodular over time. MNG develops in two different stages, which are diffuse parenchymal hyperplasia and focal somatic mutations, respectively. In the first stage, the etiology is usually iodine deficiency in endemic areas, and non-iodine factors in sporadic MNG. These stages can be seen as intertwined and their development can take many years.[28] As a result a heterogenous nodular growth is developed in MNG disease.[48–50] The nodules with different size and different functions are separated from parenchyma by fibrosis in normal thyroid tissue.[28]

Each thyrocyte tends to differ in functions and growth. This heterogeneity allows cells to be in a wide range in terms of their iodination abilities during development. As a result of this heterogeneity, some thyrocyte strains may come together to form pseudonodules, monoclonal nodules or polyclonal nodules. In addition, with the influence of genetic factors, thyrocytes can form "hot" or "cold" follicles in which iodine turnover increases or decreases according to their iodination abilities.[37]

As a result, pathogenesis of MNG encompasses diffuse follicular hyperplasia period, focal nodular proliferation period and in the end the period of gaining functional autonomy. Development of MNG is a result of corruption in thyroid hormone synthesis which is supposed to relate with long time effects of, iodine deficiency in thyroid gland, goitrogens or the other proliferative stimulants.[2]

The natural period of the growth and function in MNG is variable and unpredictible. Usually patients with MNG are euthyroid. In addition, MNG can be with hyperthyroidism or less frequently hypothyroidism. Hyperfunction is usually started with subclinical hyperthyroidism and develops in a sneaky way. That is the result of increased goiter size and related with increased volumes of cells generating thyroid hormone autonomously. Although the rates of progression from a simple MNG to a toxic NNG and the time required for this to development are not known exactly, 9–10% hyperthyroidism may develop in 7–12 years.[2]

Symptoms and Findings

Symptoms in MNG patients may develop depending on the size and function of the nodules or the total volume and location of the thyroid gland. It can be varied in a wide range from asymptomatic patients detected by physical examination or imaging methods to patients with compression symptoms, hyperthyroidism, or hypothyroidism symptoms.

It is usually seen as diffuse goiter in adolescents and young adults, but the prevalence of nodular goiter is higher in older ages.[51]

In diffuse goiter or MNG, an asymmetrical appearance is possible on inspection. With this aspect, goiter disease can be manifested with only cosmetic problems without causing any other symptoms. Although rare, patients may present with sudden pain and a rapidly developing swelling in the neck after hemorrhage in the thyroid nodule.

Table 1. Table of goiter by the WHO according to palpation examination[52]

Grade	Feature
0	Non-visible or palpable goiter
1	Goiter that is palpable but not visible in the normal neck position*(the thyroid is not visually large) There is a nodule in thyroid but thyroid gland is not large
2	Visible swelling in normal neck position and enlarged thyroid on neck palpation

It is considered as goiter if the size of each thyroid lobe is larger than the distal phalanx of the patient's thumb

Goiter related symptoms can be classified as local symptoms due to the thyroid gland size and location or systemic symptoms independent of gland size.

Upper air-way obstructions may be occurred according to the size or intrathoracic location of thyroid gland. In general, in this case, patients have difficulty in using clothes with narrow collar and describe an aggravated dyspnea in the supine position. Stridor, hacking cough, shortness of breath may be described due to tracheal compression. Especially stridor is an important symptom of serious tracheal obstruction.[28] Separation of these symptoms from non-goiter related airway symptoms is necessary. In addition, upper gastrointestinal system symptoms such as dysphagia may occur due to more increased size or the location of nodule. Goiter related dysphagia is usually associated with enlargement of the Zuckerkandl tubercle or retrosternal goiter.[36] Again, depending on the nodule location or the volume of the gland, hoarseness may be seen rarely due to inferior laryngeal nerve (recurrent laryngeal nerve) paralysis. With the further enlargement of the thyroid volume, the major vascular structures that provide venous return to the heart may be compressed.

Systemic symptoms are related to thyroid gland function and may occur with symptoms of hypothyroidism or hyperthyroidism. Hyperthyroidism includes symptoms such as increased appetite, intolerance to hot weather, irritability, agitation, tachycardia, diarrhea, muscle weakness, fatigue, sleep disorders, and dysmenorrhea. In hypothyroidism, there are symptoms such as decreased appetite, weight gain, depression, constipation, cold intolerance, fatigue, and amenorrhea.[36] In the present review, we are discussing the non-toxic MNG disease, so systemic symptoms will not be discussed in details. However, hypothyroidism and hyperthyroidism symptoms should be asked in the anamnesis of patients with goiter.

During the physical examination of the patient, local and systemic findings should be questioned in detail, just like the examination of symptoms. Findings of hyperthyroidism and hypothyroidism due to a functional disorder should be noted as an initial step. During the physical examination, information about the structure and function of the thyroid gland or possible malignancy findings can be obtained.

While communicating with the patient, attention should be paid to voice quality as a clue of possible inferior laryngeal nerve palsy or tracheal compression. Then, during inspection, the patient's neck should be observed first in its natural position and then in extension. A possible neck mass or venous engorgement should be noted. It is possible to see the thyroid gland when the patient is asked to swallow, and a possible skin retraction may be the first sign of muscle invasion. In addition, an upward mobile nodule seen in the superior part of cricoid cartilage when the patient is asked to stick out his/her tongue can be a sign of a thyroglossal duct cyst.[28]

With palpation; dimensions, location, sensitivity, mobility of the thyroid gland; size, consistency of thyroid nodules; pathological lymph nodes, if any, can be examined. During the physical examination, the patient's upper chest and posterior neck triangles should be open. In this way, a possible lymph node metastasis can be palpated.

Goiter is classified as a simple table by the WHO according to the palpation findings.[52]

When a mass on the neck is palpated with palpation, if the lower border of this mass cannot be palpated up to the sternal notch, retrosternal goiter should be suspected. During the extension, the patient is asked to drink water, hyperextend or wait 30 s with the arms folded over the head. In these maneuvers, the lower and posterior border of the thyroid gland can be palpated, as the intrathoracic part will rise. In addition, flushing of the skin and prominence of the external jugular vein during these maneuvers indicate a positive Pemberton sign. If the patient also has retrosternal tracheal compression; dyspnea and stridor may develop during these maneuvers.[37]

Clinical Evaluation

After a detailed physical examination of MNG patients, other diseases that may present with similar symptoms should be excluded. Pressure-related findings such as hoarseness, dysphagia, and stridor should be evaluated if present. In general, stridor or dysphagia indicates tracheal narrowing

and esophageal compression in severely enlarged goiters. The thyroid functions of the patient should be evaluated and it should be determined whether there is a functional disorder. It is important to examine the patient's history and family history in detail. A history of radiation to the neck area in the past or the presence of thyroid cancer in the family members is important clues for the physician. Investigation of malignancy is one of the most important steps in clinical evaluation. Although the majority of nodules in MNG are benign, MNG can be associated with thyroid cancer. In studies, malignancy rates in MNG are reported to be between 7.5% and 15%, and it increases to 20% in endemic regions.[53–56]

After the diagnosis of malignant or benign disease is made, the treatment/follow-up method such as medical follow-up or surgical treatment should be determined. If it seems necessary for the patient, additional preoperative examination and imaging might be used for the most accurate and adequate surgical procedure should be performed at the right time.

Biochemical Evaluation

In a patient presenting with MNG disease, serum TSH should be seen in the first evaluation. A TSH value in the normal range indicates that the patient is euthyroid. In these patients, TSH value lower than the normal range constitutes an indication for scintigraphy.[57,58]

There are also authors who recommend routinely monitoring T4 at the 1st time.[37] If TSH is not within the normal range, T3 and T4 should be seen definitely.

In the study by the German Society of Endocrine Surgeons, it is recommended that preoperative calcium value should be checked to exclude a concomitant parathyroid disease.[59]

Monitoring calcitonin level in the preoperative period is controversial. Calcitonin has an important role in the detection of medullary thyroid carcinoma and its preoperative level may affect the extent of the surgical procedure to be performed. However, in this respect; there are some disagreements between the American Thyroid Association (ATA) and the European Thyroid Association (ETA). ATA advocates that routine calcitonin measurement in the preoperative period may not be cost-effective, and there is no definite recommendation for the routine use of this test.[58] ETA, on the other hand, recommends routine monitoring of serum calcitonin level despite its cost.[60]

Imaging Methods

USG

High resolution imaging for evaluation of thyroid parenchyma and thyroid lesions is provided by the proximity of the thyroid gland to the skin surface on the neck.[61]

USG should be the first choice of imaging method in the evaluation of MNG patients. In many clinics, USG is frequently used for the first imaging method due to its easy accessibility, lower cost, non-invasiveness, and non-ionization method. However, the disadvantage of USG is that it is dependent on the experience of physician.

Thyroid volume, shape, and location of the thyroid can be seen with USG. In addition, the shape, location, size, characteristic structure, and vascularization of the nodule can be seen in thyroid nodules and can be a good guide for the differentiation of benign or malignant nodules.[62] Thyroid sonography is one of most used imaging methods for the evaluation of thyroid nodules to determine malignancy risks and the need for fine needle aspiration (FNA).[61]

USG features associated with the risk of malignancy in thyroid nodules have been described. These features are; capsular invasion, presence of metastatic lymph node, prominent hypoechogenic nodule, nodule that is all or mostly solid, taller than wide shape in the anteroposterior section, infiltrative or lobulated margin, punctate echogenic foci (microcalcifications), irregular or interrupted peripheral calcification.[61]

Entirely cystic composition, spongioform composition, mixed cystic–solid nodules with concentric solid portions, large comet tail, and reverberation artifact are features of very low malignancy suspicion on USG.[61]

However, any of these USG features alone do not have sufficient predictive value in predicting malignancy. If a nodule has more than one feature suggestive of malignancy at the same time, the specificity increases, but the sensitivity becomes unacceptably low. These features do not conclusively prove malignancy, but they may suggest malignancy.[62]

Risk classification systems have been developed by many national and international thyroid societies according to USG features of thyroid nodules.[58,63-66]

In order to estimate the risk of malignancy, the ATA divided the USG features into five categories as benign, very low suspicious, low suspicious, intermediate suspicious, and high suspicious. According to these features, the estimated risk of malignancy is <1%, <3%, 5–10%, 10–20%, and 70–90%, respectively.

High-risk features include a solid hypoechoic nodule or a partial cystic nodule with a solid hypoechoic component and at least one or more of the following features; irregular border (infiltrative and microlobule), microcalcifications, taller than wide shape, discontinuous, and intermittent calcification with soft-tissue protrusions, extrathyroidal extension.

Intermediate-risk factors on USG are solid hypoechoic nodule with smooth margins without features, as extrathyroidal extension, microcalcification, and taller than wide shape.

Low-risk features are isoechoic or hyperechoic solid nodules or partially cystic nodule with eccentric solid areas without features as microcalcification, irregular margin, extrathyroidal extension, and taller than wide shape.

Spongiform or partially cystic composition without any of the sonographic features is demonstrated as very low risk features (Nodule should not have any high risk, intermediate risk or low risk features.).

Purely cystic nodules (with no solid component) are described as benign nodule.[58]

However, the ATA risk grading does not categorize some nodules, such as especially high-risk features with isoechoic and hyperechoic nodules. Thyroid Imaging, Reporting and Data System (TI-RADS) classifications have been proposed by some associations.[64-66]

ETA have defined EU-TIRADS, The Korean Society of Thyroid Radiology have defined K-TIRADS, and American College of Radiology have defined the ACR TI-RADS system.[64-66]

Recently, the performance of the five risk classification systems, mentioned above, was compared according to the characteristics of 502 nodules that underwent fine needle aspiration biopsy (FNAB). In this study, five USG risk classification systems before biopsy classified biopsies as unnecessary with a false negative rate of 2.2–4.1%, and biopsies were classified as unnecessary at a rate of 17.1–53.4%, and it was found that they showed great differences in their ability to reduce the number of FNABs. Furthermore, ACR TIRADS was outperformed the others through classifying more than half of the biopsies as unnecessary with a false negative rate of 2.2%.[67]

In the study of Seminati et al.,[68] in which EU-TIRADS and ACR-TIRADS classifications were compared, it was found that the specificity of ACR-TIRADS was higher in the evaluation of Bethesda III and higher nodules.

The ACR TI-RADS risk classification system classified nodules into five categories, scoring them according to their composition, echogenicity, shape, borders, and echogenic focus. TR-1 is 0 points, TR-2 is 2 points, TR-3 is 3 points, TR-4 is 4-6 points, and TR-5 is >7 points. The malignancy suspicion described for TR-1, TR-2, TR-3, TR-4, and TR-5 as no suspicion, benign, minimally suspicious, moderately suspicious or highly suspicious, respectively.[66] And the estimated malignancy risks are 0.3%, 1.5%, 4.8%, 9.1%, and 36%, respectively.[69]

Furthermore, suspicious lymph nodes in central and lateral neck compartments should be evaluated with USG, too. The features considered malignancy suspicion in lymph nodes can be listed as enlargement, loss of fatty hilum, a rounded rather than oval shape, hyperechogenicity, cystic change, calcifications, and peripheral vascularity. For detection of metastatic lymph node, there is no single USG feature with enough sensitivity.[58]

USG, which guides us in the thyroid parenchyma, nodule characteristics, and lateral region lymph nodes, is not the ideal choice in evaluating central region lymph nodes.[70]

In the TIRADS classification, nodules are scored according to their structure, echogenicity, shape, borders and echogenic foci.

USG can also be considered a guide for FNAB in lymph nodes suspected for malignancy. FNAB performed with USG gives more accurate results compared to the results of FNAB performed with the blind technique.[71]

The location of the nodules in MNG disease may affect the surgical procedure. USG is also important in terms of eliminating the need for bilateral total thyroidectomy (TT) in patients with nodules in one lobe. However, it should not be forgotten that the performance of USG is limited in MNG patients with retrostenal extension and it should be kept in mind that cross-sectional imaging methods may also be required when necessary.[72]

Ultrasound elastosonography (USE) is a method that has emerged recently, and it is predicted that it can be used for the differentiation of malignancy, especially in nodules with suspicious/unclear results, by determining the stiffness and consistency of the nodules in MNG patients. As a newly developed technique, USE emerged by evaluating the stiffness of the nodule in response to an external pressure on the nodule with a qualitative scale. Then, quantita-

Table 2. ACR-TIRADS classification[69]

ACR-TIRADS	Score	Classification	Recommendation	Risk of malignancy
TR1	0 points	Benign	FNAB not required	0.3%
TR2	2 points	No suspicion of malignancy	FNAB not required	1.5%
TR3	3 points	Mild suspicion of malignancy	≥1.5 cm follow-up; ≥2.5 cm FNAB	4.8%
TR4	4–6 points	Moderate suspicion of malignancy	≥1 cm follow-up; ≥1.5 cm FNAB	9.1%
TR5	≥7 points	High suspicion of malignancy	≥0.5 cm follow-up; ≥1 cm FNAB	35%

ACR-TIRADS: American College of Radiology - Thyroid Imaging Reporting & Data System.

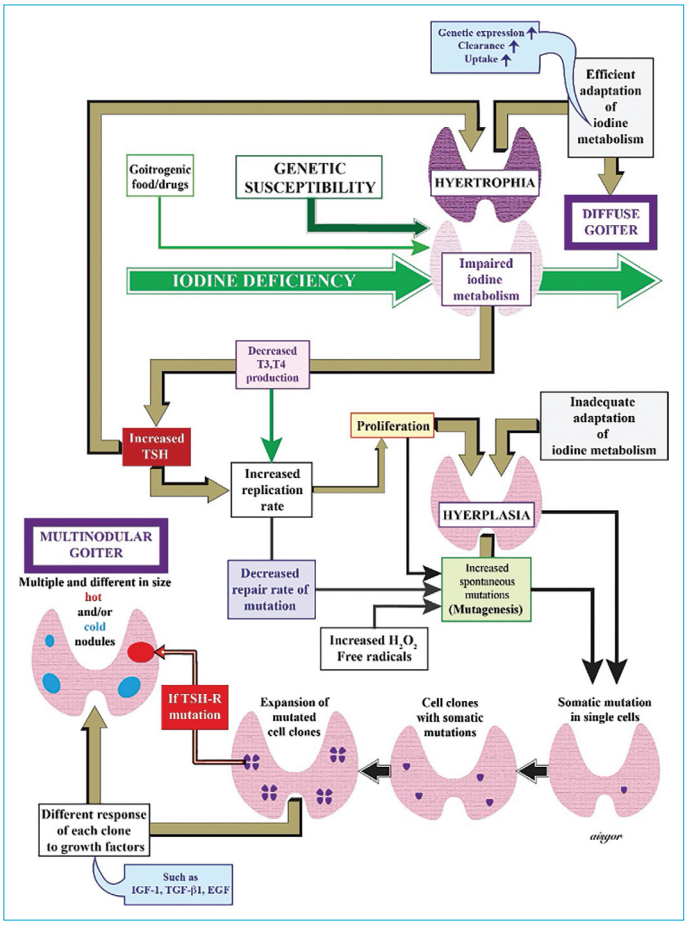

Figure 1. MNG Pathogenesis.

MNG: Multinodular goiter, TSH-R: Thyroid Stimulating Hormone Receptor, IGF-1: Insulin-like growth factor 1, TGF-β1: Transforming growth factor beta 1, EGF: Epidermal growth factor.

tive methods were discussed in USE, and an elasticity index measured according to the surrounding tissues was used first. In the method developed in recent years, the vibration response depending on the elasticity of the tissue by giving low-frequency stimulation with the ultrasound probe is a promising and practitioner-independent method.[73]

The main limitations of TIRADS and FNAB are indeterminate and non-diagnostic nodules. In these nodules, malignancy rises to such high rates that it cannot be ignored. It is expected that the use of USE will take an important place especially in indeterminate and non-diagnostic nodules.[72]

Cross-sectional Imaging Methods

Although cross-sectional imaging methods (Computed Tomography [CT] and Magnetic Resonance Imaging [MRI]) are not routinely used, they can be used in cases which USG is insufficient, such as retrosternal goiter, retroesophageal goiter, and relation to intrathoracic vascular structures. Cross-sectional imaging methods can be used in addition to USG when a possible tracheal stenosis or local invasion is considered.

Although the CT images; the degree and direction of displacement of central structures such as trachea, esophagus, larynx, and pharynx caused by the mass effect and compression effect of MNG can be explained in detail. In particular, the size of the thyroid, its borders, the neurovascular structures surrounding the thyroid gland; relation with surrounding structures including the retropharyngeal space and the prevertebral space should be evaluated. In addition, findings of possible vocal cord paralysis such as asymmetry of the vocal cords and the other findings that may be occurred due to the effect of pressure should be evaluated.[74]

In addition, the coexistence of MNG and malignancy should be evaluated. Clues of malignancy are invasion rather than central compression and the presence of abnormal cervical lymph nodes.[74]

CT procedure with intravenous contrast agent which contents iodine is contraindicated in some MNG patients due to the iodine uptake related Jod Basedow Syndrome. In the other hand, cross-sectional imaging methods are not suggested for routine because of their costs.[75]

The number of comparative and accurate studies with reliable results on the use of the MRI method compared to CT is insufficient. MRI has limited benefits for the evaluation of nodular volume or characteristics in MNG patients.[2]

CT should be performed to determine the intrathoracic extension of the thyroid in substernally located MNG. Since the operation position in thyroidectomy is with arms down and neck in extension position; neck CT should be performed with a similar position. CT should not be performed with the arms up or the neck flexed. The thyroid is positioned lower than normal in these positions, potentially misleading the surgeon and causing unnecessary sternotomy rather than a simple low neck incision.[74]

In benign MNG patients, retrosternal goiter that does not exceed the arcus aorta can usually be operated with a cervical incision. However, to determine the masses extending more caudally, cross-sectional methods should be used. Through, the surgeon could be prepared for additional procedures such as sternotomy with routine procedure.

Scintigraphy

Thyroid scintigraphy is not routinely used in the initial evaluation. In this method, which is applied using Tc99m and I 131, basically the function of the thyroid gland is evaluated, not the anatomy. It is indicated in patients with goiter who have TSH suppressed or hyperthyroidism findings in their examinations (Recommendation 1-A).[76] In scintigraphy images, we obtain four patterns. The diffuse homogeneous one is seen in Graves' disease, the one with patchy uptake

areas is in toxic MNG, the one with increased uptake area in a single point and no other uptake area in the remaining parenchyma is seen in a toxic nodule, and the pattern in which the uptake is widely reduced is seen in thyroiditis or exogenous T4 uptake.[28]

After scintigraphy performed and it should directly be compared to the US images to determine functionality of each nodule. FNA should then be considered only for those isofunctioning or nonfunctioning nodules, among which those with suspicious sonographic features should be aspirated preferentially (Recommendation 13-B).[76]

Positron Emission Tomography (PET)

The use of PET in MNG patients is negligible. In this method, which works with the principle of measuring increased glucose metabolism, malignant nodule/benign nodule can be differentiated. Nodules that were determined incidentally in PET images and found to have malignancy after surgery have been reported in the literature.[77] However, the difficult accessibility, high cost, and ionizing radiation of this method limit its use in MNG patients.

FNAB

FNAB is one of the most cost-effective procedures that guide the selection of surgical procedures and the differentiation of benign and malignant nodules in MNG patients. Although it guides on the treatment path in patients who are considered for surgery, the indications for FNAB in MNG patients are still controversial. Although this nodule is the most important candidate for biopsy in patients with a dominant nodule, in patients with multiple nodules with similar characteristics, samples should be taken from those whose USG features are suspicious, not only by the diameter of the nodule but also by other characteristic features. The risk of malignancy is very low in patients with similar low suspicious nodules and nodules without moderate or high suspicious features, and biopsy can be taken from the largest nodule in these patients or they can be followed without FNAB.[58]

In present, FNAB indications in patients with nodular goiter are clearer and the ACR TIRADS classification is seen as a successful guide in the follow-up of nodules and FNAB indications.[66] Although the number of nodules to be biopsied in MNG is controversial, the American Association of Clinical Endocrinologists guideline does not recommend FNAB from more than 2 nodules.[63]

In addition, FNAB can be applied to suspicious lymph nodes under USG; It is extremely effective in detecting a possible locally advanced tumor or lateral metastasis.[59]

In the samples taken by FNAB method, cytology is not only studied but also thyroglobulin washing is performed in this sample when its necessary. Through it increases the sensitivity of biopsy in cases where there is suspicion, whether the biopsy material is thyroid tissue or whether there is a tissue belonging to the lymph node or whether there is metastasis in the lymph node.[78]

Treatment

There is no consensus regarding the ideal treatment of MNG. The course of MNG is variable and individual. Therefore, treatment options should be evaluated individually for each patient, taking into account factors such as risk-benefit relationship, patient preference, and the experience of the treating physician.[2,51]

Treatment options in MNG:

- Clinical Follow-up
- Levothyroxine Suppression Treatment
- Radioactive Iodine Treatment
- Surgical Treatment

Clinical Follow-up

Asymptomatic patients who are euthyroid, do not have suspicious nodules in terms of malignancy, and have no cosmetic problems can be followed up clinically after clinical, laboratory, and imaging evaluation.

In most cases, clinical and US examination and TSH measurement are appropriate in 12–24 months, dependent on the clinical features and nodule volume growth. In patients with stable US features and size, subsequent clinical controls may be performed at 2-year intervals.[63]

Levothyroxine Suppression Treatment (L-T4 Treatment)

There are conflicting results in the literature on L-T4 suppression therapy. It is a method generally used in European and Latin American countries, and its success is still questioned. Although a 20–40% reduction in goiter size was observed in 12-month follow-ups in non-toxic MNG patients, it was observed that they returned to the same dimensions after treatment.[51]

It has been shown that L-T4 suppression therapy is more effective especially in diffuse goiter patients than in MNG patients.[79]

The effect of L-T4 suppression therapy is dependent on the TSH suppression dose. In a double-blind and randomized study conducted by Güllü et al.,[80] there was a 15% regression in the 9-month follow-up in patients who received suppression therapy and a 20% increase in the follow-ups in the placebo group.

In addition to the conflicting results found in the literature,

despite the moderate response to L-Thyroxine therapy, potential skeletal, and cardiac side effects outweigh the in many patients, so it is not routinely recommended in the recently published guidelines, especially in iodine-sufficient areas.[58,63]

However, it has been stated that L-thyroxine treatment with iodine supplementation can be considered in young patients with small nodular goiter and without functional autonomy living in regions with iodine deficiency. In addition, appropriate L-thyroxine treatment is recommended in patients with subclinical hypothyroidism and nodular goiter.[63]

Radioactive Iodine Therapy (RAI)

Although RAI treatment is a more frequently used method in toxic MNG patients, it has been used for approximately 30 years in non-toxic MNG patients.[51]

It is a treatment method that can be used in patients who are not suitable for surgery due to comorbidities or who refuse surgery. In this method, which is basically based on ablation of the thyroid gland by holding radioactive iodine, the treatment dose may vary, since the thyroid gland will have less iodine uptake in non-toxic MNG patients.

RAI treatment shows a higher success rate than L-thyroxine treatment, shows a significant regression in gland size in MNG patients, and appears to be significantly more successful than L-thyroxine, especially in regression of obstructive symptoms such as dyspnea and difficulty in swallowing.[81-83]

In the previous years, Hegedüs et al.[84] showed a regression of up to 40% after RAI treatment in their 1-year follow-up in 1988.

Although transient hyperthyroidism was observed in some patients during the first 2 weeks of RAI treatment, permanent hypothyroidism was observed in 45% of these patients during follow-up.[83]

Studies to increase the effect of RAI treatment, especially in non-toxic MNG patients, have continued in the past, and it has been shown that the effect of RAI can be increased by the discovery and inclusion of human recombinant TSH (rhTSH) in this way. Thanks to rhTSH increasing the affinity of RAI on the thyroid gland and also potentiating the effects of RAI; same treatment effect with the lower RAI dose or higher success rate with same doses could be determined.[85-88]

With the combination of RAI and rhTSH, 35–56% more reduction in thyroid volume was detected than with non-stimulated RAI treatment.[63]

Although it has been suggested that there is a decrease in dose-dependent side effects and the risk of radiation-induced malignancy after RAI is given together with rhTSH, this is not clear.[89,90]

The main long-term complication of rhTSH administration is the increased rate of hypothyroidism. The risk of postoperative hypothyroidism increases up to 5 times in patients who use rhTSH compared to those who do not use rhTSH.[63]

As a result, in nontoxic MNG, rhTSH and RAI treatment provide a greater reduction in thyroid volume, while the risk of hypoparathyroidism increases.[91]

After RAI treatment, especially in the first 48 h, one should be prepared for findings such as dyspnea due to an increase in goiter size, difficulty in swallowing, swelling, and tenderness in the goiter area, and tachycardia. Painful thyroiditis or thyrotoxicosis after treatment is usually seen within 1 month. The incidence of hypothyroidism afterward in these patients is higher than in those without symptoms. In addition, Nygaard et al.[92] showed in their study that antibody positive Graves' hyperthyroidism may develop after RAI treatment in euthyroid patients.

- Surgical Treatment
- Surgical Indications

Main surgical indications in non-toxic MNG patients;[93]

- Large goiter size or enlargement in follow-up,
- Compression symptoms (Dyspnea, Pemberton's sign, Dysphagia, and similar findings),
- Substernal goiter
- Malignant or suspected malignant nodule,
- Visual reasons

Although surgical indications are generally elective in non-toxic MNG, emergency surgery may rarely be required. Intrathyroidal or intranodular hemorrhage, postoperative bleeding, rarely infections, inflammatory conditions that may cause sudden parenchymal enlargement may result in respiratory arrest, especially in patients with respiratory system problems such as underlying chronic obstructive pulmonary disease.[94,95]

Surgical Procedure and Its Extent

MNG is the disease that most frequently requires surgical intervention, and debates about its optimal treatment have been ongoing for many years.[96]

Different methods have been accepted as standard in thyroid gland surgery over the years. Although sub-TT was defined as a safe method with fewer complications in the past for the surgical treatment of bilateral nontoxic MNG, more radical surgeries such as TT and/or near-TT (NTT) have be-

come preferred at the beginning of this century.[97,98]

Theodor Kocher, one of the pioneers of goiter surgery, was performing TT in MNG patients at first. Over time, he saw myxedema developing in the postoperative period in these patients. Thyroxine preparations were not yet used at that time, and Kocher defined TT as "an operation that should be condemned" and turned to sub-TT.[99]

After Kocher, Australian surgeon Thomas Dunhill performed the bilateral subtotal thyroidectomy (BST) procedure. However, Cecil Joll was the first to publish BST in his book "Thyroid Gland Diseases." This surgery was considered the gold standard until thyroxine preparations were discovered. After the discovery of thyroxine, some surgeons continued to advocate this procedure, stating that the potential complications would be lower.[99]

In the 1950s, Francis Rundle founded the Sydney Thyroid Surgery Unit and, after Thomas Reeve joining the team, performed more than 5000 operations, most of them benign MNG and Graves' disease. It was stated that a surgery less than TT would be insufficient in MNG patients when the relapse and recurrence rate in the follow-ups was noticed to be much higher than the acceptable rate. With the advancement of technology and the increase in evidence-based studies, TT has started to be accepted as the first choice in MNG patients.[96,100-102]

Since the beginning of the 2000s, TT has become the first preferred surgical option in the treatment of bilateral MNG.[97,98]

In the pathological examination after sub-TT, the rate of incidental thyroid cancer is found to be between 3% and 16.6%, and the recurrence rate is up to 50%.[96]

Especially in patients with incidental thyroid cancer detected after BST, the need for completion thyroidectomy is significantly higher than in TT and NTT.[97]

In a retrospective cohort study involving more than 8 thousand patients, the rate of completion thyroidectomy for incidental thyroid cancer in BST compared to TT in MNG was higher (2.15% vs. 0.1%; p<0.001, respectively). Furthermore, the recurrence rate in patients with BST was 6.99%. Of these, 45.33% required reoperation and the reoperation rate was significantly higher in BST than in TT (3.14% vs. 0, respectively, p<0.001). Permanent complication rates were similar.[103]

In a literature review evaluating the studies published between 1987 and 2007, the rate of temporary hypoparathyroidism is higher in TT compared to sub-TT (9–35% vs. 0–18%, respectively. There was no difference in terms of temporary (1–10% vs. 0.9–6%, respectively) and permanent (0–1.4%) recurrent laryngeal nerve palsy (RLNP) and permanent hypoparathyroidism. The recurrence rate was higher in sub-TT (2.5–42%) than in TT (0–0.3%). In redo surgery, compared to primary surgery, both temporary (0–22% vs. 0.5–18%, respectively) and permanent (0–13% vs. 0–4%, respectively) RLNP and permanent hypoparathyroidism (0–22% vs. 0–4%, respectively) were higher. The researchers stated that TT is a surgical option that eliminates recurrence without increasing permanent complication rates in the surgical treatment of MNG.[104]

In a prospective randomized study evaluated the 10-year follow-up results of TT, BST, and Dunhill procedure (DP) techniques in the surgical treatment of MNG. The 10-year recurrent goiter rate was 0.6% versus 8.6% versus 22.4% after TT, DP, and BST, respectively (p<0.001). The recurrence rate in TT was lower than both DP (p<0.001) and BST (p<0.001). In addition, the recurrence rate was lower in DP than in BST (p<0.001). Reoperation rate for recurrence was 0.6%, 2.9%, and 8% in TT, DP and BST, respectively, and reoperation rate in BST was higher than both DP (p=0.019) and TT (p<0.001).

Total permanent complication rates after first and revision surgery were 2.8% versus 4% versus 5.7% for TT, DP, and BST, respectively. Investigators recommended TT as the preferred intervention in the treatment of MNG, as it does not increase the total permanent complication rate and eliminates the risk of recurrence and reoperation.[105]

In addition, they found that the 10-year results of DP and BST were 2 times worse than the 5-year results in terms of recurrence and need for reoperation, and there was no difference for TT.[105,106]

Other advantages include rapid regression of symptoms and determination of the histological diagnosis of the entire gland in TT compared to subtotal resection. It has been proven that there is no significant difference in complications between the two procedures when performed by experienced endocrine surgeons in experienced centers.[107-111]

In an adequate TT, it is aimed to completely remove the thyroid gland and leave no residual tissue. In subtotal thyroidectomies performed to reduce the risk of complications, especially the posterior elements of the thyroid lobe (such as the Zuckerkandl tubercle) are deliberately left behind. The most common cause of persistent symptoms and recurrence after BST is the remained Zuckerkandl tubercle.[102]

Endocrine surgeons need to have a good grasp of not only the anatomy of the region but also the embryology. The pyramidal lobe is the most common recurrence site for embryological reasons after TT. In terms of recurrence, this region is followed by the thyrothymic remnant and Zuckerkandl tubercle. Therefore, considering the thyroid tissue in these regions is important in terms of recurrence risk.[28]

However, in recent years, more conservative resections have been recommended instead of TT by some researchers.[112]

Contrary to the studies discussed above, another prospective randomized study reported that the risk of recurrence and reoperation with small remnants after both BST and DP was low in 10 years of follow-up, and both methods were safe in benign thyroid surgery.[113]

Mauriello et al.[112] stated that the indications for MNG should be discussed clearly due to the high rate of postoperative hypoparathyroidism, especially after TT. Particularly, they claim that partial resections such as DP or sub-TT are surgical alternatives in benign MNG surgery that provide a lower complication rate and a small nodule-free thyroid remnant. They mentioned that recurrence can be prevented and less postoperative complications, better functional status, and an insignificant risk of recurrence can be achieved especially with DP and postoperative L-thyroxine treatment.

However, it is clear that randomized controlled studies with high evidence value are still needed for a clear conclusion on this subject.

A personalized surgical decision will need to be made in all patients. In general, surgical treatment for MNG is applied to young patients. These patients have a long life expectancy after surgery. Especially in patients who will undergo bilateral surgery, advantages or disadvantages of leaving residual tissue in the thyroid lodge should be evaluated especially in terms of reoperation. The recurrence rate increases as the follow-up period increases after subtotal resections.[105,106]

According to the Delbridge et al.,[109] recurrence-related reoperations peak at the 13th year.

The risk of complications increases up to 20 times in interventions performed for recurrence.[114]

In unilateral MNGs, unilateral lobectomy is a suitable option and the recurrence rate is low in the postoperative follow-up.[115,116]

Compared to TT, the need for L-T4 replacement is also significantly lower in lobectomy.[116]

In patients who underwent lobectomy, morbidity does not increase when surgery is performed if recurrence develops in the contralateral lobe.[117]

In conclusion, during decision of surgical treatment the patient's indication for surgery, the bilateral and unilateral nature of the goiter is important factors to be considered in the extent of surgery. Lobectomy is a rational option in unilateral MNG. In bilateral MNG, performing a TT without leaving any remnant tissue that may cause recurrence in the thyroid lodge is a suitable option. Particularly in the patient with asymmetric goiter and small nodules on one side for which there is no indication for surgery, the option of lobectomy to the lobe with a surgical indication, can be discussed with the patient.

Benign non-toxic MNG is one of the most common endocrine diseases affecting the population today, and different treatment modalities are applied. Indications that direct surgeons to operate with this disease are usually compression symptoms, suspicion of malignancy, cosmetic concerns, and ineffectiveness of other treatments.[118]

As the number of treatment methods increases and the tendency to make joint decisions with the patient increases, the effect of these methods on the quality of life has become increasingly important.[119]

Many different scales have been used to investigate the effects of these diseases and treatment methods on the quality of life, and we can generally group these scales under two main headings: The effect on the general quality of life and the effect on the disease-specific quality of life.[120]

Many scales such as ThyPRO, SF-36, SF-12, PCS, MCS, EuroQoL, SWAL-QOL, WLQ, SCL-90 R, and EORTC QLQ can be used under these two subgroups. The most commonly used scale to assess the overall quality of life in benign non-toxic MNG patients is the SF-36 questionnaire, and the most frequently used method to assess the disease-specific quality of life is ThyPRO.[120]

Although post-surgical complications affect the quality of life negatively, contradictory results about goiter disease and treatment methods emerge when these studies, which are already few in the literature, are evaluated in terms of the effect on general quality of life.[121]

Although it was seen in the study of Mirallié et al.[122] that post-operative complications cause deterioration in professional activities, it is seen that there is no effect on the general quality of life when examined with the SF-36 questionnaire.

However, in the study of Sorensen et al.,[123] improvement on the quality of life of the patients with recurrent nerve palsy in the regression of the symptoms of goiter was 11 points lower compared to the patients without complications.

In the systemic review and meta-analysis of Chaves et al.,[118] studies using the ThyPRO questionnaire were evaluated and it was shown that surgery provided a significant improvement in the effect on disease-specific quality of life compared to the preoperative period.

In the review, significant improvement was observed especially in goiter symptoms, fatigue, depression, emotional state and anxiety, and these results suggest that quality of life is more affected especially in surgeries performed for

tracheal compression, esophageal compression, increase in goiter size, and cosmetic reasons.[124]

Weight Gain after Surgery

There is a common belief in the population that weight will be gained after thyroid surgery. Progressive age-related weight gain may continue with the previous thyroid surgery. However, the effect of thyroidectomy alone on weight gain is controversial.

There are studies in the literature showing that there is weight gain after surgery, especially in patients with hyperthyroidism. When this situation is investigated, it is understood that weight gain is not a condition related to thyroid surgery, but should be interpreted as the disappearance of the effects of hyperthyroidism in the preoperative period.[125]

On the other hand, the situation in euthyroid patients may be a little more complicated. In the literature, it is seen that there are conflicting results in studies that are generally designed as retrospective.

In the study published by Weinreb et al. in 2011, 102 thyroid cancer patients who underwent TT and 92 benign nodular goiter patients who were followed up medically were followed for a median of 5.9 years, and no significant difference was observed in terms of weight gain. In this study, patients were not grouped according to age, gender, and effects of TSH suppression.[126]

In a recent study published by Glick et al., it was stated that TT has no effect on weight gain, and patients can gain weight, lose weight, or continue at the same weight after thyroidectomy; it has also been stated that there is no predictor to foresee these situations.[127]

Although there is a common belief that patients will gain weight after TT, studies published in the literature to date do not provide a clear view on this issue. More studies are needed for the possible effects of thyroidectomy on weight gain or loss, especially in non-toxic patients.

Metabolic Syndrome in Post-Surgical or Non-operative Patients

Thyroid hormones have an important effect on basal metabolism of the thyroid gland, especially due to their direct effects on carbohydrate metabolism and lipid metabolism.[128-130]

Especially after thyroidectomy or in patients with thyroid dysfunction, predisposition to metabolic syndrome may occur after the effects of thyroid hormones on metabolism are removed.

With its increasing incidence, metabolic syndrome has now become an important public health problem in the general population. Although it is seen at different rates in different locations, this disease, which has complications that can cause mortality, is becoming increasingly common all over the world.

In a study of 1422 Caucasian non-toxic MNG patients published by Rendina et al., this disease was determined as an independent risk factor for metabolic syndrome.[131]

Again, studies assessing the relationship between goiter disease and metabolic syndrome have shown that subclinical hypothyroidism may lead to metabolic syndrome.[132-134]

Although it is thought that L-thyroxine replacement after thyroid surgery may prevent the development of metabolic syndrome, Zihni et al.'s study revealed that metabolic syndrome may develop after TT despite L-thyroxine replacement.[135]

In this study, it was observed that the incidence of metabolic syndrome increased from 39% to 52% in the postoperative 1st year after TT, and increased to 62% in the 2nd post-operative year; It was found that this rate reached 92% in patients with TSH level >4.2 m IU/mL in their 2nd year.[135]

It is recommended that L-thyroxine therapy and metabolic syndrome parameters be followed closely in the postoperative period in patients who will undergo TT. In addition, it should not be forgotten that this picture may occur in non-operative follow-up in patients with thyroid dysfunction. Non-TT or other medical treatment methods can be considered, although rare, especially in diabetic, high body mass index, hypertensive patients due to a possible predisposition to metabolic syndrome.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.T.U., M.U.; Design – M.T.U., M.K., N.A.; Supervision – M.U., A.I.; Materials – None; Data collection &/or processing – M.T.U., M.K.; Analysis and/or interpretation – N.A., M.U.; Literature search – M.T.U., M.U., A.I.; Writing – M.T.U., M.K.; Critical review – N.A., A.I., M.U.

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