

## Review Paper

## Total Insights on Goiter in Children: A Mini-review



Setila Dalili<sup>1</sup>, Daniel Zamanfar<sup>2</sup>, Afagh Hassanzadeh Rad<sup>3\*</sup>, Saber Najafi Chakoosari<sup>4</sup>

1. Pediatric Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran.
2. Diabetes Research Center, Department of Pediatric Endocrinology, Mazandaran University of Medical Sciences, Sari, Iran.
3. Pediatric Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran.
4. Student Research Committee, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.



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## ABSTRACT

**Background:** Thyroid disorder is one of the main endocrine problems in childhood. In children with thyroid disorders, goiter is common.

**Objectives:** In this mini-review, the authors aimed to present total insights on goiter in children.

**Methods:** This is a mini-review about total insights on goiter in children. This review included articles assessing goiter in children. Web of Science, PubMed, and Google Scholar were investigated to find appropriate articles regarding goiter in children from 1988 to 2021. The keywords were thyroid, goiter, hyperthyroidism, hypothyroidism, and thyroid nodule. The authors included all study types assessing the pathophysiology, evaluation, and treatment of goiter in childhood.

**Results:** Through taking the medical history and performing a physical examination, clinicians can differentiate types of goiter, including diffuse or nodular toxic or non-toxic, which can present themselves in euthyroid, hypothyroid, and hyperthyroid states. When taking a medical history, clinicians have to ask patients about their food intake, place of residence, and nutrient deficiencies to abstain from goitrogens. Diverse treatment methods are required for goiter in euthyroidism, hypothyroidism, and hyperthyroidism. In patients with euthyroidism, whenever there is iodine deficiency, a history of irradiation to the neck, or Hashimoto's disease, suppressive therapy is needed. Both clinical and subclinical hypothyroidism need levothyroxine. Besides, in hyperthyroidism, antithyroid drugs, iodine therapy, or surgery are needed. Both clinical and subclinical hypothyroidism need levothyroxine.

**Conclusions:** In hyperthyroidism, antithyroid drugs, iodine therapy, or surgery are needed. Based on the importance of managing goiter in children, clinicians have to consider food intake, vitamin deficiency, and iodine status in these patients.

\* Corresponding Author:

**Afagh Hassanzadeh Rad, MD.**

**Address:** Pediatric Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran.

**Tel:** +98 (133) 3369002

**E-mail:** afaghrad@gums.ac.ir

## 1. Introduction

**T**he thyroid is a small, butterfly-shaped gland with two lobes that are placed in the neck under Adam's apple. Thyroid disorder begins from birth (congenital hypothyroidism) and occurs due to diverse risk factors [1]. It is one of the main endocrine problems in childhood as well. In children with thyroid disorders, goiter is common [2]

Goiter is the enlargement of the thyroid gland and is commonly caused by autoimmune diseases, colloid goiter and also iodine deficiency occur in children and adolescents, but congenital goiter can be due to a wide range of disorders, including effects from transplacental transfer of maternal antibodies or goitrogens and drugs, genetic disorders as inborn errors of thyroid hormone production, congenital anomalies, or iodine excess or deficiency [3-5]. It can be diagnosed by physical examination or ultrasound assessment. Although using ultrasound is the gold standard for diagnosing goiter, it is costly in remote parts of low-income countries where goiter assessments are highly required [6]. The physical examination can be an alternative to ultrasonography in all patients except iodine-deficient ones. Assessing the prevalence of goiter in mild iodine-deficient patients showed that goiter is not detected in 23.9% of children by palpation and there is a discrepancy between palpation and ultrasound results. Therefore, it seems that palpation is relatively inaccurate for indicating the goiter in mild iodine deficiency and ultrasound is a useful tool for this condition [7]. However, it is believed that in normal iodine levels, performing the physical examination is associated with similar accuracy to ultrasound. Generally, in children >5 years old, the physical examination can diagnose goiter when the size of each lobe of the thyroid gland is larger than the terminal phalanges of the thumb [8]. In this mini-review, the authors aimed to present total insights on goiter in children.

This is a mini-review about total insights on goiter in children using articles assessing goiter in children. Web of Science, PubMed, and Google Scholar were investigated to find appropriate articles regarding goiter in children from 1988 to 2021. The keywords were thyroid, goiter, hyperthyroidism, hypothyroidism, and thyroid nodule. The authors included all study types assessing the pathophysiology, evaluation, and treatment of goiter in childhood.

Since performing a physical examination in goiter can be an alternative for ultrasonography in all, except

iodine-deficient, patients, in this review, the authors explained the history of physical examination noted by the World Health Organization (WHO), the evaluation of thyroid by ultrasonography, and the evaluation of iodine deficiency.

### Physical examination of the thyroid (WHO)

In 1960, the WHO released the criteria for the classification of thyroid size, including four grades of goiter. Goiter 0 indicates no palpable or visible goiter. Goiter 1 indicates that the goiter is palpable but it is not visible when the neck is in the normal position. Goiter 2 indicates a noticeably enlarged gland when the neck is in the normal position. Goiter 3 indicates a visible gland at a distance of 10 meters.

In 1994, the WHO redefined the classification. It mentioned goiter as a palpable and/or visibly enlarged thyroid gland. By the latter redefinition, in some cases, smaller thyroids can be indicated as goiter as well [6]. Although the latter was easier than the former classification, it is believed that the detailed 1960 version is more applicable [9].

### WHO Classification/Grading

- 0: No goiter
- 1a: Palpable lobe
- 1b: Noticeable gland on neck hyperextension
- 2: Gland noticeable with the neck in normal position
- 3: Visible gland at a distance of 10m

### Revised Goiter Grading

- 0: Thyroid is not enlarged by inspection or palpation
- 1: Goiter is palpable, but not seen when head and neck are in normal position
- 2: Thyroid is visible when the head is in normal position and is enlarged on palpation

### Application of ultrasound in goiter

Ultrasonography can be used for small goiters to estimate the number, size, and sonographic characteristics of nodules. Although the characteristics of ultrasound in graves and Hashimoto's disease is non-specific, hypoechogenicity, microcalcifications, macrocalcifications,

intranodular vascularity, taller-than-wide dimensions, and blurred margins can guide clinicians to differentiate benign and malignant nodules [8, 9].

#### Measurement of thyroid volume by ultrasonography

Ultrasonography for thyroid volume is used by the formula of a rotation ellipsoid model. It is estimated as width x length x thickness x 0.52 for each lobe and Table 1 shows the volumes based on age [4, 10]

#### Evaluation of iodine deficiency

Iodine is a vital nutrient for the synthesis of thyroid hormones. It is essential for normal reproduction, growth, and development. Although Iodine Deficiency Disorder (IDD) is one of the main health problems worldwide, according to the previous investigation, its prevalence is decreasing recently [2]. Low dietary iodine intake is one of the main factors resulting in IDD and goiter is the most visible sign of IDD [4].

Four methods, including urinary iodine concentration, the goiter rate, serum Thyroid-Stimulating Hormone (TSH), and serum thyroglobulin are usually used for the measurement of iodine [11, 12]. Recent iodine intake (days) can be measured by urinary iodine [13] and serum thyroglobulin indicates the intermediate response (weeks to months). The goiter rate shows long-term (months to years) iodine intake [14]. Among these methods, the median urinary iodine concentration that indicates recent iodine intake is the principal indicator of IDD [13].

Although neonatal TSH screening is a routine method in monitoring IDD in mothers and babies, WHO recommended adding other methods for monitoring IDD in a geographical area [15]. Therefore, integrating urine iodine concentration and TSH results is suggested. WHO classified medians of urinary iodine concentration as below:

1. <20 µg/L: insufficient and severe IDD
2. 20-49 µg/L: insufficient and moderate IDD
3. 50-99 µg/L: insufficient and mild IDD
4. 100-199 µg/L: adequate and optional
5. 200-299 µg/L: more than adequate
6. >300 µg/L: risk of adverse consequences [16].

In neonatal TSH screening, if the first TSH level is  $\geq 5$  mIU/l, the subjects would be recalled for more evaluation. The recalled results are classified based on the percentage of neonatal TSH as below:

- Non-IDD: <3
- Mild IDD: 3-20
- Moderate IDD: 20-40
- Severe IDD: >40 [16].

#### Pathophysiology of goiter

The pathophysiology of goiter divides into three domains of stimulation, inflammation, and infiltration. Stimulation includes increased TSH or activated receptors by antibodies (grave's disease) or activated G-protein (McCune-Albright syndrome). Inflammation includes acute and subacute thyroiditis that can be infectious or non-infectious. Infiltration includes malignancy, histiocytosis, thyroiditis lymphocytic, and tuberculosis [5].

#### Evaluation of goiter by taking history and physical examination

##### A) Taking history

For evaluating goiter, clinicians should first take a medical history based on the features of hypothyroidism and hyperthyroidism. Then, the evaluation of food intake, place of inhabitants, and deficiency of micronutrients that affect the physiology of the thyroid for producing thyroid hormones are necessary. Thus, family history of thyroid disease, consanguinity, geographical area of residence, exposure to irradiance, medication history, goitrogens, and in newborns, history of maternal exposure to iodine or antithyroid drugs and symptoms suggestive of hypothyroid or hyperthyroid states because of maternal grave's or autoimmune thyroid disease should be asked [17, 18].

In addition, goiter or thyroid disease in siblings, especially if there is no history or clues of maternal autoimmune disease should be asked. Then, the presence of goiter or thyroid disease in an older (or twin) sibling suggests a heritable disorder (dysmorphogenesis in the presence of hypothyroidism and an activating mutation of the TSH receptor or the G protein stimulatory alpha subunit in the presence of hyperthyroidism) [4].

**Table 1.** Thyroid volume in children [5]

Age (y)	Mean±SD
7	3.1±1.3
8	3.3±1.2
9	3.6±1.3
10	4.0±1.5
11	4.9±1.5
12	5.3±1.4
13	6.1±1.6
14	6.3±1.5

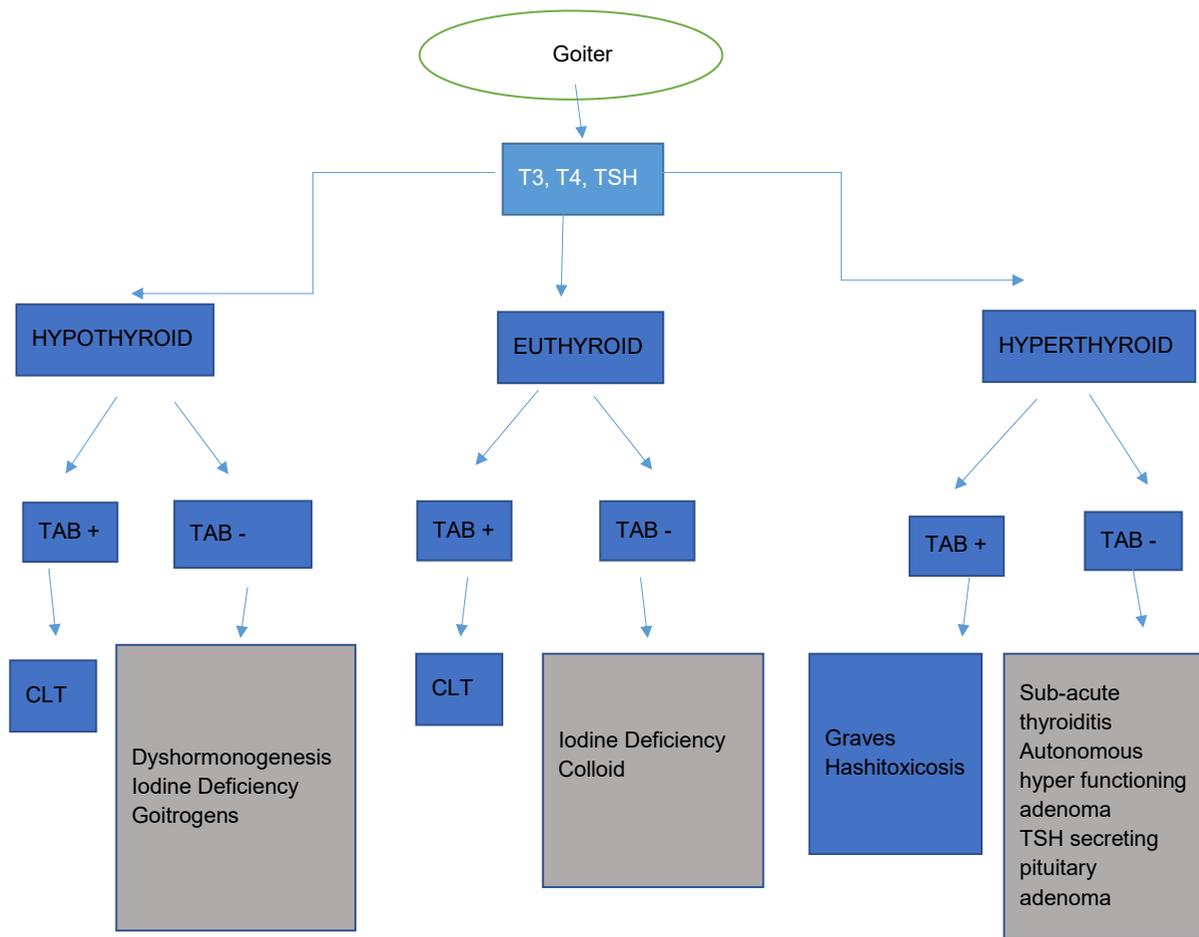
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**Table 2.** The differential diagnosis of goiter

Congenital Goiter	Acquired Goiter
<p>Hypothyroid in infants Elevated TSH levels, low or normal levels of free T4: Prenatal antithyroid drug treatment Dyshormonogenesis: Genes are the sodium-iodide symporter (SLC5A5), thyroid peroxidase (TPO), dual oxidase 2 (Duox2), and its accessory protein (Duoxa2), thyroglobulin (Tg), iodotyrosine deiodinase 1 (IYD), and pendrin (SLC26A4). The SLC26A4 variants also cause sensorineural hearing loss, known as pendred syndrome (25). Iodine excess, iodine-rich drugs, such as expectorants, amiodarone, nutritional supplements, iodinated radiocontrast agents, and oil-soluble iodinated contrast (26). Iodine deficiency and iodine-deficiency goiter can occur in neonates, but it is rare (27).</p> <p>Hyperthyroid in Infants (suppressed TSH, elevated or normal free T4 levels) TSH receptor-stimulating antibodies: Goiter may be present due to transplacental passage of TSH receptor-stimulating antibodies (Graves' disease). Other Causes: Congenital goiter and hyperthyroidism without TSH receptor-stimulating antibodies indicate one of the following causes, which can be distinguished by specific molecular testing: Activating mutation of the TSH receptor mutations that can cause diffused goiter and hyperthyroidism, referred to congenital nonimmune hyperthyroidism (28). McCune-Albright Syndrome It is caused by somatic activating mutations of the TSH receptor or G protein stimulatory alpha subunit (29).</p> <p>Euthyroid in Infants (normal TSH and free T4 levels) Thyroid hemiagenesis It may cause unilateral goiter in neonates (30). Thyroglossal Duct Cysts Most of them are in the midline, but they can occur anywhere along the thyroglossal duct (31). Thyroid Neoplasm Thyroid teratomas are present in the neonatal period (32).</p>	<p>Euthyroidism status Chronic autoimmune (Hashimoto's disease) thyroiditis Colloid goiter Thyroid neoplasm (benign adenoma, carcinoma) Acute suppurative thyroiditis</p> <p>Hypothyroid status Excess iodine ingestion (in health food supplements or drugs, e.g., amiodarone) Ingestion of other goitrogens or drugs (e.g., tyrosine kinase inhibitors and checkpoint inhibitors) Iodine deficiency Thyroid infiltrative disease (histiocytosis and cystinosis) Subacute granulomatous thyroiditis (de Quervain disease)</p> <p>Hyperthyroid status Graves' disease Autonomous ("hot") nodule Toxic multinodular goiter Subacute granulomatous thyroiditis (de Quervain disease); early differential diagnosis will be based on TSH levels and antibodies</p>

\* TSH: Thyroid stimulating hormone

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**Figure 1.** Algorithm for evaluating goiter in hypothyroidism, euthyroidism, and hyperthyroidism

TAB: Thyroid antibody (anti-thyroid peroxidase (TPO) antibody).

CLT: Chronic lymphocytic thyroiditis.

TSH: Thyroid stimulating hormone.

The history, especially in children and adolescents, should include the time of onset, duration of goiter, and change in size or characteristics, such as nodule formation [5].

**B) Physical examination**

A general physical examination should be done, including vital signs, and look for symptoms/signs suggestive of hyperthyroidism, such as excessive sweating, high blood pressure, tachycardia, tremor, exophthalmos, or hypothyroidism as growth failure, lethargy, constipation, dry and puffy skin, and weight gain [19].

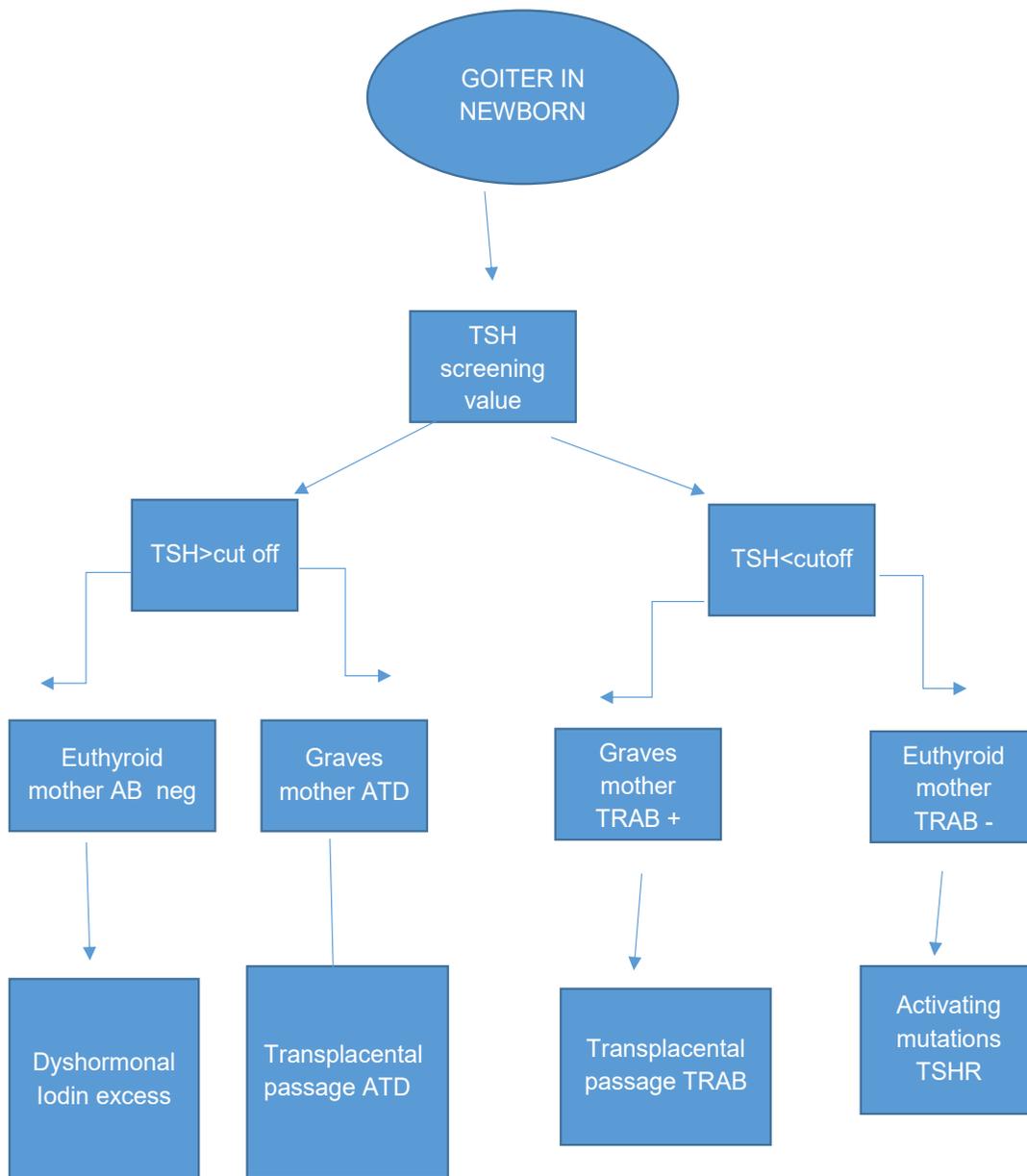
Then, the neck and thyroid are examined for nodularity, consistency, surface and texture, signs of compression, lymphadenopathy, bruits, scars, symmetric or asymmetric enlargement of the thyroid, diffuse or nodular enlargement, neck swelling, erythema, and

tenderness or pain over thyroid lobes, and softness of goiter or nodule.

Using this information, clinicians can differentiate different types of goiter as diffuse, nodular, suppurative thyroidism, probable malignancy, euthyroid, hypothyroid, or hyperthyroid [5, 19].

**Food intake**

Clinicians have to ask patients about their food intake because some foods are goitrogens and patients should abstain from taking these foods. Lima beans, linseed, sorghum, cassava, and sweet potato are cyanogenic glucosides that are metabolized to thiocyanates. Because they compete with iodine uptake, they can induce goiter. Soy and millet have flavonoids. Flavonoids can impair thyroid peroxidase activation and cause goiter [20]. Cruciferous veggies, including cabbage, kale, cauliflower-



**Figure 2.** Algorithm for evaluating goiter in newborns

AB: Antibody  
 TSH: Thyroid stimulating hormone  
 ATD: Antithyroid Drug Therapy  
 TRAB: TSH receptor antibody  
 TSHR: Thyroid stimulating hormone receptor

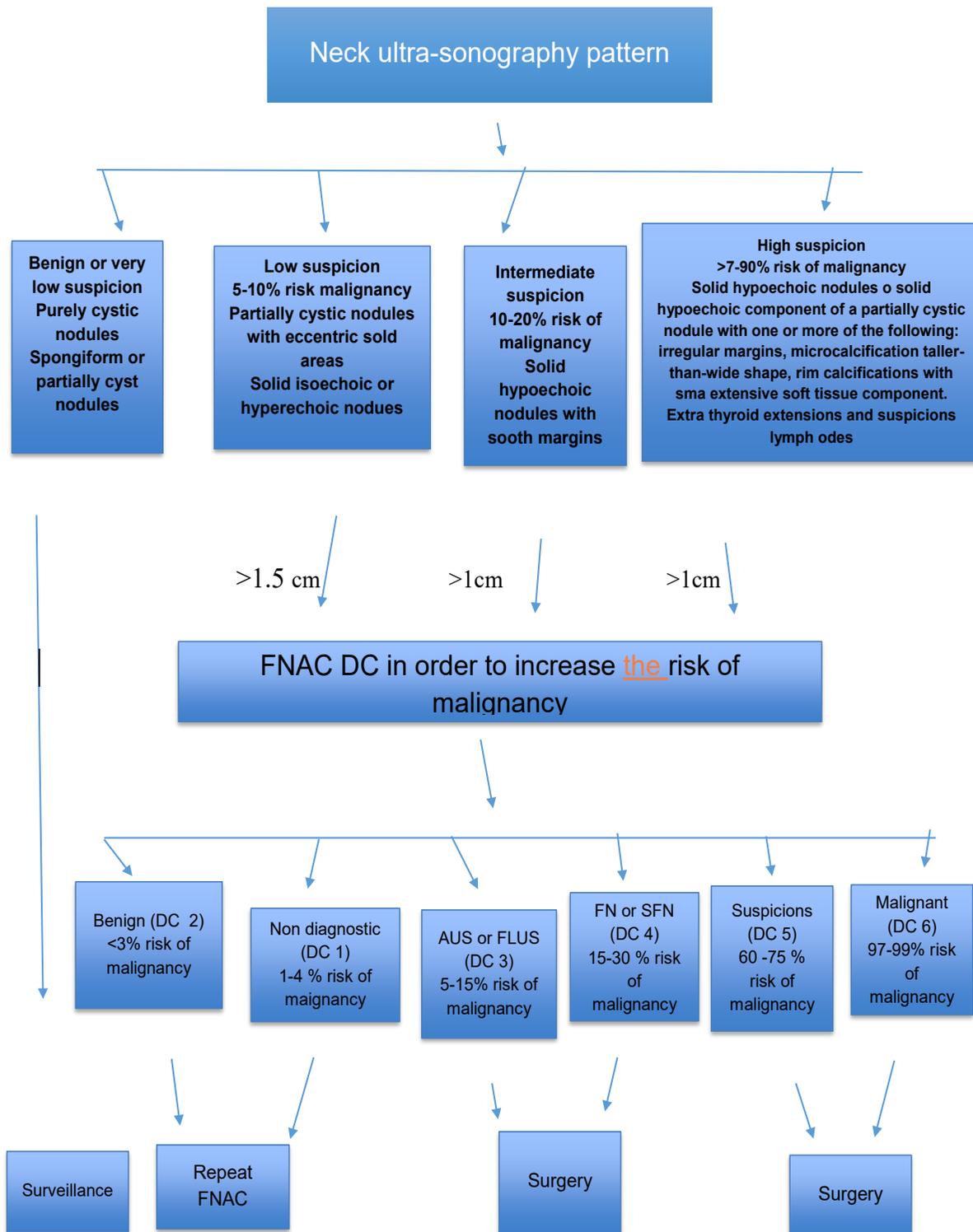
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er, broccoli, turnips, and rapeseed have glucosinolates and compete with iodine for thyroidal uptake; therefore, their use is prohibited [21].

**Place of inhabitants**

Place of residence is an important issue in children with goiter. Children living in places with industrial pollutants, such as perchlorate, disulfides (coal products),

and those exposed to smoking are at higher risk of goiter. Perchlorate is a competitive inhibitor of sodium/iodide symporter that decreases iodine transport into the thyroid. Disulfides reduce thyroidal iodine uptake and can cause goiter. Smoking is goitrogenic and exposure to smoking in breastfeeding can reduce iodine concentration in breast milk. It also has thiocyanates that compete with iodine for active transport into the secretory epithelium of the lactating breast [22].



**Figure 3.** The neck ultrasonography approach to nodules.

FNAC: Fine-needle aspiration cytology  
 AUS: Atypia of Undetermined Significance  
 FLUS: Follicular Lesion of Undetermined Significance  
 FN: Follicular neoplasm  
 SFN: Suspicious for follicular neoplasm  
 DC: Diagnostic category

## Micronutrients

Taking a thorough history is important because selenium, iron, and vitamin A deficiencies can cause goiter. Selenium deficiency can cause accumulated peroxidase and damage the thyroid. Deiodinase deficiency impairs the synthesis of thyroid hormones. Iron deficiency decreases heme-dependent thyroperoxidase activity in the thyroid and may blunt the efficacy of iodine prophylaxis. Moreover, vitamin A deficiency elevates TSH stimulation and goiter. Decreased vitamin A mediates suppression of the pituitary TSH beta gene [20].

## Etiology and differential diagnosis of goiter

Congenital and acquired goiter can be differentiated in the differential diagnosis of goiter (Table 2) [23]. In terms of congenital hypothyroidism, measuring the TSH might reveal the causes along with the results of the history and antibody tests in most cases [22-32]. Besides, acquired goiter causes can be categorized into three different groups.

## Evaluation of goiter by laboratory results

As mentioned above, the evaluation of goiter is based on several factors. Diffuse goiter can either be toxic or non-toxic. Non-toxic goiter is thyroid gland enlargement with no disturbance in the thyroid function. It is not due to inflammation or neoplasia [33], unlike toxic goiter that causes hormone imbalance. The same story goes for nodular goiter. It can either be single or multinodular as well as toxic or non-toxic. For further evaluation of these two types, several tests must be performed as follows:

**Diagnostic tests for diffuse goiter:** First, diffuse goiter was divided into two groups of asymptomatic and hypothyroidism and the hyperthyroidism group. Serum T4 and TSH levels, thyroid antibodies, and thyroid ultrasound are needed for asymptomatic diffuse goiter. In hyperthyroid diffuse goiter, serum T3, T4, and TSH levels, thyroid antibodies, thyroid ultrasound, and thyroid scan should be assessed.

**Diagnostic tests for nodular goiter:** Serum T3, T4, and TSH levels, fine needle aspiration, thyroid ultrasound, and thyroid scan are required for asymptomatic and hypothyroid nodular goiter. In hyperthyroid nodular goiter, serum T3, T4, and TSH levels, thyroid ultrasound, and thyroid scan should be assessed.

## Algorithm for the diagnosis of acquired and congenital goiter

Patients with goiter are evaluated based on physical examinations and laboratory tests. Figure 1 shows the algorithm for evaluating acquired goiter in hypothyroidism, euthyroidism, and hyperthyroidism. Figure 2 shows the algorithm for evaluating goiter in newborns.

## Evaluation of nodules in a short overview

For patients with nodules, sonography is required for further evaluation. In benign or very low suspicion, such as purely cystic nodules and spongiform or partially cystic nodules, only surveillance is needed because they have a <3% risk of malignancies. Also, in the non-diagnostic type, repeated fine needle aspiration is needed for further evaluation. As Figure 3 shows, the sonographic pattern in neck ultrasonography and approach to nodules, surgery is the best choice for all other types, except those with low risk of malignancy and non-diagnostic type [32].

## Treatment of goiter

Diverse treatment methods are required for goiter in euthyroidism, hypothyroidism, and hyperthyroidism. In patients with euthyroidism, whenever there is iodine deficiency, a history of irradiation to the neck, or Hashimoto's disease, suppressive therapy is needed (TSH must be kept between 0.5 and 1 with the appropriate dose of exogen thyroid hormone). In patients with hypothyroidism, there are clinical (TSH > 10) and subclinical (TSH 4-10) types. Although treatment with levothyroxine is the best choice for clinical hypothyroidism, it is recommended for subclinical hypothyroidism as well. For patients with hyperthyroidism, anti-thyroid drugs, surgery, and radioiodine are mandatory.

## 2. Conclusion

Based on the importance of managing goiter in children, clinicians have to consider food intake, vitamin deficiency, and iodine status in these patients.

## Ethical Considerations

### Compliance with ethical guidelines

All ethical principles were considered in this article. The participants were informed of the purpose of the research and its implementation stages.

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### Authors' contributions

All authors equally contributed to preparing this article.

### Conflicts of interest

The authors declared no conflict of interest.

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