The problem of goitre with particular consideration of goitre resulting from iodine deficiency (II):
Management of non-toxic nodular goitre and of thyroid nodules

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Abstract
The present opinions on the therapy with L-thyroxine (L-T₄) of non-toxic multinodular, as well as of non-toxic thyroid nodules are rather divergent. This treatment is based on the suppression of TSH secretion from the pituitary.
There are no doubts that fine-needle aspiration biopsy (FNAB) performance is the first and – at the same time – the most significant diagnostic procedure in the case of thyroid structural lesions (nodules, goitre, thyroiditis). FNAB performance should – by all means – precede the beginning of L-T₄ application for the treatment of non-toxic multinodular goitre or thyroid nodules.
The simplicity, clearness and high efficacy, with comparable results in each case, are the core of good diagnostic algorithm. Unfortunately, not all diagnostic algorithms concerning thyroid nodules and multinodular goitre fulfil these important criteria.

Rather divergent views have been reported, concerning the application of levothyroxine (L-T₄) preparations in the therapy of single, non-toxic thyroid nodules and of multinodular non-toxic goitre; the nature of this treatment is suppression of thyrotropin (TSH) secretion from the pituitary, while TSH is a significant growth factor for thyroid follicular cells in vivo [1].

However, both early reports [2], and the latest observations [3] reveal that TSH is not required for thyroid growth initiation and promotion. Following this opinion, some reports indicate that TSH need not be the dominating growth factor, either for benign or for malignant thyroid tumours [3].
On one hand, the efficacy of L-T₄ suppressing effects on nodule size reduction is not certain, while, on the other, an administration of thyroid hormones in TSH secretion-suppressing doses may lead to decrease of bone mineral density, especially in postmenopausal women [4].

Women with history of either hyperthyroidism or of L-T₄ administration in TSH concentration-suppressing doses (as a therapy commonly used in the complex treatment of differentiated thyroid...
cancer – following total thyroidectomy and ¹³¹I application), should undergo bone mineral density evaluation, especially in sites with cortical bone prevalence (e.g., hip, forearm) and, however to a smaller extent, in areas with trabecular bone structure.

It should be emphasized that the thyroid hormone replacement therapy with maintained normal serum TSH concentration, has either a minimal or no effect on the bone mineral density (BMD) at all [4].

L-T₄ administration may also be a risk factor of cardiac hypertrophy [5]. Left-ventricular hypertrophy has been observed as a result of chronic L-T₄ administration in patients with no significant changes in either heart rhythm or arterial blood pressure or in left-ventricular systolic function, what suggests a direct, trophic effect of L-T₄ on myocardium [5].

Recently, several prospective studies have been analysed, concerning the effects of L-T₄ administered in TSH-suppressing doses for at least 6 months, on the sonographically-determined volume of single benign thyroid nodules [6]. The summary of obtained results indicates that patients, in whom the nodule volume decreased by more than 50%, stood for 26.5% in a group of 242 L-T₄-administered patients, while 12.3% only among 171 patients of the control group, receiving either placebo or no treatment at all. Moreover, in the control group, there was a higher percent of patients, presenting with nodular volume increase by more than 50% (17.3%), when compared with that in the L-T₄-receiving group (8.1%). Zelmanowitz et al., using cumulative metaanalysis, have drawn a conclusion that treatment with L-T₄ preparations was associated with decreasing volume of thyroid nodules in 17% of patients, while in other 10% of the patients, L-T₄ prevented the increase in volume of examined nodules [6].

According to the cited authors, an appropriate management should comprise a 12-month therapy with L-T₄ preparations, administered in suppressive doses to premenopausal women and men – in whom no cardiovascular contraindications have been diagnosed; this treatment should then be continued with slightly smaller doses of L-T₄ (relative, partial or incomplete TSH suppression), if nodular volume has decreased. Unlike in younger persons, may TSH-suppressive therapy with use of L-T₄, when applied in older age, induce undesirable side-effects, outweighing the actual therapeutic advantages. Moreover, there is a risk that such therapy may deteriorate the symptoms resulting from previous, suppression-resistant, endogenic foci of thyroid hormone production.

According to La Rosa et al. [7], in cases of single, solid thyroid nodules (scintigraphically “cold”), with diameter ≤ 3.5 cm – with the diagnostic outcome of fine-needle aspiration biopsy (FNAB) as benign – “colloid-parenchymal lesion”, an administration of L-T₄ preparations should be regarded as the therapy of choice, until the use of this hormone is contraindicated for any reason. The applied treatment should keep serum TSH concentration at levels < 0.3 mU/L, however, not around the values typical for overt hyperthyroidism (i.e., below 0.03 mU/L). Nodules with volumes > 10 mL (i.e., of diameter > 2.7 cm) will, most probably, not decrease in size after such treatment, thus their volumes should be monitored until increase. L-T₄ ought to be administered in cases of such nodules only when their further growth is observed.

In the course of treatment with L-T₄ preparations, the different types of response to this hormone can be observed, namely:

1) The nodule volume is getting reduced, what becomes visible after 4–8 months of treatment. The therapy with L-T₄ preparations should be continued until further reduction of nodular volume is observed. At this stage, the therapy may be discontinued; it may be restarted if nodule size increases again.

2) Nodule size does not change in the course of L-T₄ treatment. In this case, resistance to administered L-T₄ need not yet be suspected, as this agent may prevent further increase of nodule size. The therapy may be restarted if further increase of nodule is observed. However, if the nodule increases in size in the course of L-T₄ treatment, it should unquestionably be withdrawn.

3) The nodule volume increases in the course of L-T₄ therapy. Since non-neoplastic changes almost never increase during therapy with L-T₄ preparations, administered in TSH-suppressing doses, the observed nodule enlargement is an unequivocal indication to surgery [7].

It should be added that potassium iodide (KI) administration (especially in case of goitres resulting from iodine deficiency) may be advantageous in patients with small nodules, with diagnosed contraindications to L-T₄ therapy. Administration of KI in combination with L-T₄ may also be effective [7, 8].

Cooper [9] provides recommendations and protocols, concerning the treatment of benign thyroid nodules with L-T₄, based on nodule size variations (enlargement, stability, decrease), either in result of TSH-suppressive therapy with L-T₄ preparations or in the course of untreated patient’s observation. As an initial assumption does the author regard the known observation (almost always true) that nodule size decrease, either in result of L-T₄ therapy or spontaneous, may be approached as manifestation of benign character of nodular change.

For simplification, all the patients were divided by Cooper into the following two groups: 1) women before menopause and men, 2) postmenopausal women [9] (Fig. 1).

In both premenopausal women and in men with single thyroid nodule diagnosed by FNAB (performed at the beginning of management) as benign lesion, Cooper recommends a 12-month suppressive therapy with L-T₄, administered in such doses as to maintain TSH concentrations at the level < 0.1 mU/L [9]. If the nodule does not respond to the therapy, the thyroid hormone preparation is withdrawn and the patient is submitted to further observation. If, however, nodule enlargement is observed in the course of thyroid hormone administration, either diagnostic FNAB is to be repeated or
immediate surgical intervention is to be considered. When nodule size decreases (what can be found in palpation or following sonographic imaging), Cooper [9] suggests to provide the patient with an option between such L-T4 dose reduction as to maintain TSH concentration at lower normal values, however, with perspective of chronic (without any time limits) administration of this hormone, and therapy withdrawal, followed by observation. In the course of his recommendations, Cooper emphasizes that, in contrast to the data on multinodular goitre, there is no reliable information on clinical consequences of L-T4 withdrawal in case of thyroid nodules which had primarily decreased in result of TSH suppression by this hormone. Clinical experience indicates that some of the nodules are getting enlarged, while other remain stable.

In postmenopausal women, Cooper [9] recommends 6–12-month observation period without therapy, following FNAB indicating benign character of lesion. If, after this period: 1) the nodule remains the same or decreases in size, treatment is still withdrawn; 2) the nodule size enlarges, L-T4 therapy is applied for 12 months in doses to maintain TSH concentration below the normal values, at the same time, above the threshold of detectability by sensitive methods (>0.1 mU/L and <0.5 mU/L); 3) the nodule size enlarges in the course of L-T4 therapy, either repeated FNAB or surgical intervention is recommended [9].

After a 12-month application, the L-T4 therapy is withdrawn, regardless whether effective or not. If, after L-T4 withdrawal, nodule enlargement is observed, the therapy is restarted, using L-T4 dose to maintain TSH concentration at the lower normal limit; chronic L-T4 administration is continued for an undetermined (unlimited) period of time.

Having analysed the above considerations, Cooper [9] recommends an extreme care in the management of elderly postmenopausal women – with decreased estrogen concentrations – in order to protect them from complications in the cardiovascular system or from bone mass loss.

According to Ridgway [10], the following management is to be applied in patient with diagnosed single, solid, and cytologically benign nodule (FNAB should be the first diagnostic step!) and with normal thyroid function:

1) the patient should undergo a 12-month observation, without L-T4 therapy. At the end of the 1st year of observation, the patient should be submitted to thorough examinations, oriented towards the presence of thyroid disease symptoms; the thyroid function and nodule size should be assessed in ultrasonographic imaging [10].

2) If: A) nodule size have not changed or have decreased spontaneously, the observation without treatment should be continued; B) the nodule has increased in size, FNAB should be repeated; C) the performed biopsy has revealed either malignant process or suspicious change, the patient should be submitted to surgical intervention.

All other patients, in whom nodule enlargement has been diagnosed, should be treated with L-T4 preparations, administered in doses high enough to suppress serum TSH concentration to levels within the range of 0.1–0.5 mU/L. The observation and treatment with L-T4 preparation should be continued for subsequent year. If the nodule increases in size during L-T4 therapy, surgical intervention is necessary. Patients with neither growing nor diminishing nodules during L-T4 therapy should continue receiving this hormone.

Even if the algorithm, as proposed by Ridgway [10], is not perfect, it eliminates suppressive treatment with L-T4 preparations in patients, in whom either spontaneous involution or no enlargement of nodular changes is observed. This approach limits the application of L-T4 preparation in suppressive doses only to patients in whom therapeutic advantages are possible, i.e., patients with nodule enlargement (Fig. 2). The goal of such approach to this problem is not nodule size reduction, as much as the prevention of its enlargement and of certain symptoms associated with enlargement process;
in other words, the point is to prevent clinically overt disease (tumour enlargement) rather than to treat subclinical disease, which, according to Ridgway [10], is the presence of nodule, neither varying in size nor causing any clinical symptoms (except of its very presence). On the other hand, the acceptance of the hypothesis that suppressive treatment with L-T₄ prevents the enlargement of benign nodules in the thyroid gland, is fairly easy. At the same time, it is very difficult to prove the efficacy of this treatment in controlled prospective studies. 

Summing up, despite many reports, no unequivocal standards of management have been developed with respect to the therapy of single, non-toxic thyroid nodules or of multinodular goitre with L-T₄ preparations. 

In the background of treating single thyroid nodules with L-T₄ preparations, a number of questions can be raised, concerning the appropriate diagnostics of the thyroid gland, i.e., such diagnostics which should always be performed prior to the treatment, assessing the possibility of its application. At present, there are no doubts that ultrascan (US)-guided FNAB is the first and the most important step in the preoperative diagnostics of structural changes in the thyroid gland. Below, there is an algorithm proposed by Greenspan [11] in the widely-recognized manual of endocrinology (Fig. 3). This point of view has been confirmed by the most eminent authorities, including clinical consultants, dealing with thyroid diseases, and specialists in thyroid pathomorphology [7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26]. 

Some authors try to prove the preoperative usefulness of large needle aspiration biopsy (LNAB) of the thyroid gland, reporting that it improves the diagnostic efficacy of FNAB in cases of microfollicular nodules [27]. We do not share the view. At the same time – with respect to the thyroid gland – we warn against possible complications from the use of large needle. 

The chief point of good diagnostic algorithm is its simplicity, clearness, and high diagnostic efficacy, comparable in each diagnostic case. Unfortunately, not all algorithms fulfil the above conditions; the algorithm of management in cases of thyroid nodules in children and adolescents, proposed by Foley and Peter [28] is a negative example, being extremely complicated, casting many doubts and raising many objections.

Figure 3. Decision matrix for workup of a thyroid nodule [11].
For already quite a long time, we present an opinion that no different diagnostic algorithms are necessary for children and adults, with respect to nodular goitre, thyroid neoplasms, and thyroiditis. Diagnostic algorithm, having a universal application, should be as simple as possible and independent of patients’ age. There is no doubt in cases of nodular goitre, thyroid neoplasms and thyroiditis that the universal and simple algorithm, reported a number of times in Polish medical literature (see below), proves true in practice [29, 30, 31, 32, 33, 34, 35] (Fig. 4). This algorithm is based on either similar or identical assumptions as other algorithms, developed in many centres all over the world [9, 10, 11, 36, 37, 38], and can effectively be used in the diagnostics of the above mentioned diseases, regardless of patient’s age.

The above mentioned diagnostic algorithm [29,35] is applied in cases of:
1. single thyroid nodule;
2. multinodular goitre (in this case it is extremely useful to apply “power Doppler” or “colour Doppler” US methods, in order to properly select the dominating nodule or a few dominating nodules, which should subsequently be subjected to a FNAB in order of the potential possibility of malignancy; the most suspicious are those lesions which are characterized by the biggest blood flow rate;
3. increased consistency of the gland, detected by palpation (suspicion of the autoimmune thyroid disease);
4. goitre with distinctive pain during palpation;
5. focus/foci of changed acoustic density, impalpable, especially those with diameter above 10 mm, both in the enlarged and in normal thyroid gland; these lesions are called “incidentalomas”, which term appears to be more proper – from the logic point of view – than “impalpable nodules”.

There are also separate algorithms of diagnostic management (Fig.5), used with regards to impalpable lesions and identified in US imaging as foci of changed acoustic density (cf point no.5 above) [39]. Lesions of this type are referred to as “incidentalomatata”. As mentioned before, these, incidentally found lesions in the thyroid gland, are submitted to cytological diagnostics, depending on the degree of risk of malignant neoplasm in patient, the nature of the sonographic image of analysed focus, and on the lesion diameter [19,39,40,41]. Especially, the last criterion may be subject of controversy.

Following the generally accepted views, the differences in the incidence of particular types of pathological changes, observed in the thyroid gland in childhood (distribution of diagnoses) in comparison with data obtained in adult patients, however fairly characteristic, do not justify any different diagnostic management in children from that accepted for adults [34,39, 42, 43, 44, 45, 46, 47, 48, 49, 50].

The main differences concerning pathological changes of the thyroid in children and adolescents are as follows:
1) before the age of 18, hyperplastic lesions, both neoplastic and non-neoplastic, more often occur as a single tumour of the thyroid gland, especially nodular goitre in children is often manifested in the clinical picture as single hyperplastic nodule, raising false suspicion of adenoma or even follicular carcinoma;
2) chronic thyroiditis in childhood presents with different morphological and clinical pictures, when compared to those in adult patients. In aspirates from the thyroid gland, affected by this process, distinctive oncocytic metaplasia of follicular epithelium is extremely rare, despite of the cellular material, sometimes exceptionally rich in lymphocytes. Moreover, the course of chronic thyroiditis in children more rarely leads to the development of persistent hypothyroidism;
3) It should also be kept in mind that the diagnostics of structural lesions of the thyroid gland in childhood...
is affected by a higher risk of finding congenital malformations and developmental disorders which can manifest themselves as pathological lesions exceptionally difficult to be characterized;

4) it is a well-known fact that papillary carcinoma – in countries with high or normal iodine supplementation, during the recent years also in Poland – is the most frequently observed malignant neoplasm of the thyroid gland; in children, it stands for more than 90% of all cases of this carcinoma; it is also most frequently found in adults, standing for 75% of all carcinoma cases in Poland;

5) it is characteristic that the follicular type of papillary thyroid carcinoma in children is almost as frequently observed as the classic microscopic form of this neoplasm, while the third position in this ranking is occupied by the type with diffuse sclerosis.

Still, however, despite the above mentioned differences of child age, we claim that there is no need nor any justification for the diagnostic algorithm of detecting structural lesions in the thyroid gland to be different for children and adults.

It appears from the diagnostic algorithms, concerning cases of thyroid nodules in children and adolescents, as presented by Foley and Peter [28], and, generally, in all the patients, independently of age, as proposed by Castro and Gharib [38] (Fig. 6), that the selection of diagnostic procedures, including also the role of US-guided FNAB, depends on the functional status of the thyroid gland.

In my opinion, the data from literature on the occurrence of malignant neoplastic lesions in the thyroid gland of hyperthyroid patient (e.g., the diagnosis of cancer in “hot” nodule), although not very frequent (the coexistence rate of a few percent), justify to initiate the diagnostic process from FNAB – also in case of nodules in hyperthyroid patients and in euthyroid patients with autonomously-functioning thyroid nodules (AFTN).

In earlier reports, thyroid scintigraphy was proposed to select thyroid nodules into high-risk nodules and low-risk nodules ("cold" vs. "warm" or "hot"); FNAB was recommended only in case of "cold" nodules.
(Fig. 7). However, the same authors decided to start the diagnostic process from FNAB in cases of single, quickly growing nodules [36] or, in their subsequent published reports, they modified their approach to the problem, suggesting FNAB to be the first step in the diagnostic process [11] (the respective algorithm see Fig. 3, as shown before).

Following our opinion, the occurrence of nodular disease enforces the physician to start diagnostics from US-guided FNAB, regardless of the functional status of the thyroid gland.

If the reason of FNAB delay or – in other words – of shifting FNAB to a more backward position in the diagnostic algorithm is fear of negative psychological effects (in the child’s perception) of the biopsy, performed with the use of needle and syringe, we represent the opinion that this fear is an inappropriate consideration of health of the little patients. Many authors share our view on the significant role of FNAB as the first diagnostic study in case of thyroid nodules in children [43, 44], especially, that thyroid nodules – however much more rare in children than in adults – bear a several times higher risk of malignant process [42].

In descriptions of actual diagnostic procedures, concerning the treatment of thyroid nodules, after FNAB – performed as diagnostic study of the first order – many authors allow a possibility of periodic observation of the nodules without drug administration or recommend L-T4 as initial management – in order to assess the response of nodule to suppressive therapy. Short-term administration of L-T4 in high doses may, in this case, be treated as a specific diagnostic tool, verifying if the examined nodule can be regarded as benign; the nodules which shrink are approached as not malignant [52, 53]. Subsequent diagnostic procedures are performed only when the nodule enlarges, either spontaneously or despite L-T4 administration [7, 9, 10].

A separate comment is required for the application of thyroid scintigraphy in the diagnostics of structural lesions in the thyroid gland in its typical anatomical position, i.e., in the anterior part of the neck. Scintigraphy of the thyroid gland is a valuable study which can find applications both in the diagnostics and in treatment of thyroid diseases, especially neoplastic. However, its usefulness consists in the visualisation of iodine-uptaking tissue with untypical location (thyroid cancer metastases, thyroid malformations, ectopic thyroid tissue, aberrant goitre) than of nodules localised within the thyroid gland in its anatomically typical location.

Moreover, if any fears, associated with the use of radioactive isotopes in the diagnostics (among others, of the thyroid gland), had any justification, this would much more concern children, especially small, than adults.

Summing up this issue, we believe that, in certain algorithms, the scintigraphic examination of the thyroid is not necessarily included [28, 54]. Following the results of the “North American Survey”, dedicated to members of the American Thyroid Association), American endocrinologists apply scintigraphy of this organ three times less frequently than their European colleagues [55, 56]. Also worth emphasising is the much less importance of sonographic imaging of the thyroid gland among American authors than it is in Europe [10, 13, 55, 56].

The simpler are all standards of management, diagnostic and therapeutic, the better they are in practice. They should also be legible for physicians who are not specialists in a given medical branch. In the actual reality, an addition to the diagnostic algorithm of, for example, scintigraphic examination, what may be regarded necessary by physician not specialising in endocrinology, will certainly prolong the time of diagnostics, delaying cytological examination by several months.

Figure 7. Decision matrix for the work-up of the thyroid nodules [51].
On the margin of considerations on the design of all diagnostic algorithms, a rather important problem emerges, namely, whether it would be justified that the calculation of probability, determining the risk of pathological change, affected the shape of diagnostic scheme. This can be illustrated by the following example: papillary thyroid carcinoma may grow in the gland multifocally and not in the form of single tumour. Therefore, should there be any arbitrarily determined borderline of the lesion, imaged in sonographic examination, above which FNA should be performed? This last problem may be regarded as specific self-criticism [32, 33], although, on the other side, we have to admit that also other authors recommend in their algorithms arbitrarily determined borderlines for the size of diagnosed lesions [39, 40].

In summary, it should be stated that the main goal of the preoperative diagnostics of thyroid tumours is the quickest and the most accurate selection of cases which should be surgically treated. The same goal is assumed by the preoperative cytological diagnostics of multinodular goitre [57]. Such an understanding of this issue raises two important questions:

1) is it possible to select high-risk patients on the basis of knowledge of cancer pathogenesis and its epidemiology?

2) can our knowledge in this respect be applied for the prevention of cancer?

At the end, I would like to emphasise that any evaluation of thyroid cytology, as well as any other diagnostic and/or therapeutic procedures, concerning thyroid nodules, should be adjusted to the level of iodine consumption by the population in a given geographic territory [58, 59]. Moreover, it should be remembered that the aspiration process, even with thin needle, may change, however slightly, the volume of thyroid nodules, what complicates the interpretation of L-T4 therapy efficacy in suppressing TSH concentrations [18].

Below, I would like to present the classification of cytological diagnoses, developed for practical use in my research group [34, 50].

Groups of cytological diagnoses:

GROUP I – The cytological picture is characteristic enough to make an unequivocal diagnosis of specific disease entity:
- undifferentiated carcinoma
- papillary carcinoma
- subacute granulomatous thyroiditis
- suppurative acute thyroiditis

GROUP II – Cytological picture with accurate clinical data allows to distinguish a definite disease entity:
- medullary carcinoma
- malignant lymphoma
- cyst
- nodular goitre
- metastatic neoplasm
- chronic thyroiditis (i.e., Hashimoto’s disease)

GROUP III – Cytological picture and clinical data allow to draw the differential-diagnostic circle:
- follicular neoplasm – follicular tumour
- oncocytic tumour
- benign tumour – benign lesion
- chronic inflammatory reaction

GROUP IV – The outcome is confined to a description of aspirated material, sometimes with additional remarks on further diagnostic-therapeutic management but no definite diagnosis can be made.

GROUP V – Cytological picture unequivocally indicates that the punctured structure/lesion is not pathologically changed thyroid:
- lymph node
- salivary gland
- parathyroid
- muscular tissue
- fat tissue
- tracheal elements (ciliary (respiratory) epithelium)
- teratoma

The last report, the results of which I would like to present, should not find improper applications; it was proved not so long ago that alcohol consumption was associated with lower incidence of goitre and of single thyroid nodules [60]. It is difficult to say whether this is an optimistic perspective but, just at this point, I would like to finish this short review of prevailing opinions on the conditions for the diagnostics and therapy of thyroid nodules with L-T4 preparations.

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