

The problem of goitre with particular consideration of goitre resulting from iodine deficiency (I): Classification, diagnostics and treatment

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Abstract

In the present review paper, the following problems have been brought up:
1) types of non-toxic goitre and applied classification,
2) physiological periods or states predisposing to non-toxic goitre development,
3) evaluation of excessive stimulation of the thyroid gland,
4) the treatment of iodine deficiency consequences (non-toxic diffuse vs. non-toxic nodular goitre),
5) autoimmunologically-induced non-toxic goitre, and
6) positive effects of iodine prophylaxis with respect to goitre prevalence.
The management of non-toxic nodular goitre, as well as of thyroid nodules is a separate and very complex issue, and – at the same time - the subject of our next review paper, published in the same issue of NEL.

Types of non-toxic goitre and applied classification

The most frequent effect of iodine deficiency is non-toxic goitre, i.e., goitre unaccompanied by thyroid function disorders. Depending on either the absence or the presence of nodules, diagnosed during palpation, non-toxic goitre can be divided into diffuse and nodular, respectively.

The classification of goitre, used in the 80s of the 20th century, with regards to its size determined by palpation [1], is the following:

- Grade 0 – no goitre presence is found (the thyroid impalpable and invisible);
- Grade 1a – the thyroid gland, however palpable, remains invisible, even in full extension of the neck (the thyroid not enlarged);
- Grade 1b – goitre – palpable in normal position and visible in the upright position (full extension) of the neck; nodular goitres are also classified into this size range, even if they do not meet the criteria of enlarged thyroid gland;
- Grade 2 – goitre – visible in normal position of the neck; no palpation required to diagnose thyroid enlargement;
- Grade 3 – very large goitre, clearly visible from distance.

The actually standing and simplified classification of goitre, as proposed by the WHO [2], refers to the following criteria:

- Grade 0 – no goitre presence is found (the thyroid impalpable and invisible);
- Grade 1 – neck thickening is present in result of enlarged thyroid, palpable, however, not visible in normal position of the neck; the thickened mass moves upwards during swallowing. Grade 1 includes also nodular goitre if thyroid enlargement remains invisible.
- Grade 2 – neck swelling, visible when the neck is in normal position, corresponding to enlarged thyroid – found in palpation.

It should be emphasized that sonographic evaluation of the thyroid size is more accurate in comparison with palpation, being especially recommended in children with small goitre.

The diagnosis of nodular goitre results from palpable examination, i.e., finding of uneven, nodular thyroid surface. The palpable uneven areas correspond to, so-called, hyperplastic nodules, usually present in enlarged thyroid gland. The hyperplastic nodules in nodular goitre are characterized, among others, by the lack of complete connective tissue encapsulation, no distinctive morphological signs of pressure, exerted by the nodules on the adjacent parenchyma of the thyroid gland, what differentiates hyperplastic nodules from neoplastic ones. Thus, nodular goitre is a benign, non-neoplastic lesion and – even if it has been assigned to Class VII in Hedinger *et al.*'s classification of thyroid tumours (1988) [3] – then, it has been defined in its class as “tumour-like lesion”, what corresponds to its actual character. The palpably diagnosed nodular character of thyroid enlargement places the goitre – regard-

less of its actual size – in, at least, grade 1b in the classification from 1986 [1].

The presence of foci with varied echogenicity, observed in sonographic imaging, which, however, are not palpable, is not the basis for the diagnosis of nodular goitre; it is impossible to reveal occurrence of such foci only by palpation. The management of the, so called, thyroid incidentalomas, will be discussed in detail in our next review paper, published in the same issue of NEL.

Nodular goitre may be either the subject of treatment with L-thyroxine or of surgical intervention [4].

Physiological periods or states predisposing to non-toxic goitre development

Predispositions to thyroid enlargement are observed in puberty, pregnancy, and physiological lactation, especially in territories of decreased – vs. requirements – iodine supplementation or in those with overt iodine deficiency. The tendency towards thyroid enlargement during growing and maturation of the organism is associated with an enhanced requirements for thyroid hormones and – with respect to girls – with the puberty-accompanying hyperestrogenism, leading to hyperglobulinaemia, resulting in elevated concentrations of protein-bound thyroid hormones, thereby in the relative decrease of the concentration of the free thyroid hormones. In conditions of insufficient iodine supplementation, relative hypothyroxinaemia appears, leading to the increased concentration of thyrotropin (TSH) – the main growth factor for the thyroid gland. The presented process is the most essential mechanism of goitre development in result of iodine deficiency. Similarly, predisposition to thyroid enlargement in gestation is mainly observed in territories with iodine deficit [5]. The risk of goitre development in pregnant women concerns patients both with normal thyroid function [6] and with mild, subclinical disorders of the function in question [7].

In the territories with decreased iodine supplementation, significant enlargement of the thyroid gland has been observed in women during pregnancy, only partial goitre size reduction in the postpartum period, and coexistence (together with thyroid enlargement) of biochemical indices of excessive thyroid stimulation [5, 6, 8]. The tendency towards thyroid enlargement in pregnant women results from the additional load, exerted onto the secretory function of the gland, caused – on one hand – by enhanced requirements for thyroid hormones (with a simultaneous relative decrease of their production with respect to the actual needs), and – on the other – by decreased availability of iodine for mother's thyroid. The increased demand for thyroid hormones, observed in the organism of pregnant woman, results from changes in hormonal balance (hyperestrogenism) and protein metabolism (hyperglobulinaemia).

Increased requirements for thyroid hormones in pregnancy are also observed in women with hypothy-

roidism, treated with levothyroxine (L-T₄) preparations as replacement therapy; in this case, the daily dose of L-T₄ should be increased of 40–50% vs. that applied before gestation [9].

Patients with normal thyroid function and with the presence of antithyroid autoantibodies (antithyroglobulin – anti-Tg and/or antithyroperoxidase – anti-TPO) manifest a higher predisposition towards subclinical hypothyroidism during gestation [10]. Thus, iodine deficit plays an important role during gestation, leading to an excessive stimulation of this gland and, in consequence, to relative hypothyroxinaemia and goitre formation [11].

Evaluation of excessive stimulation of the thyroid gland

The phenomenon of excessive stimulation of the thyroid gland is found mainly in areas with iodine deficiency; it was also commonly observed in Poland before the implementation of the widespread model of iodine prophylaxis with iodized kitchen salt. An excessive stimulation of the thyroid gland in pregnant women, as well as in other adults and children, can be traced in clinical practice, taking into account the following four biochemical parameters [12].

1. relative hypothyroxinaemia, i.e., incommensurably small elevation of total thyroxine (TT₄) vs. the increase of the concentration of thyroid hormone-binding globulins (Thyroxine Binding Globulins – TBG) in blood serum during the 1st trimester of pregnancy; it should be added that the concentration of free thyroxine (FT₄) presents with values close to the lower normal level in about 1/3 of patients;
2. preferential secretion of triiodothyronine (T₃) in result of excessive thyroid stimulation in conditions of iodine efficiency; it is reflected by an increased molar T₃/T₄ ratio;
3. serum TSH concentration which – in result of the elevation of hCG concentration in the initial stage of pregnancy – is gradually decreased, then – from about the 10th week of gestation, because of gradual decrease of hCG concentration, increases again up to the values from before pregnancy;
4. thyroglobulin (Tg) concentration which is elevated already in the 1st trimester of pregnancy in about 1/3 of patients, getting higher in subsequent weeks of the 2nd and the 3rd trimester; increased Tg concentration has been observed in about 2/3 of patients. An increase of serum Tg concentration may be a useful marker in the prognosis of goitre development during pregnancy.

The assessment of the clinical value of particular biochemical markers is especially important to demonstrate the excessive stimulation of the thyroid gland and, consequently, the tendency towards thyroid enlargement.

It should be assumed that, at present, the incidence of elevated markers of excessive thyroid stimula-

tion will gradually be decreasing among the population inhabiting the territory of Poland.

The treatment of iodine deficiency consequences – non-toxic diffuse goitre

The main differences between the actual recommendations of therapeutic management in cases of non-toxic goitre and the recommendations from the year 1997 [13, 14, 15, 16, 17, 18], i.e., before the implementation of the widespread model of iodine prophylaxis, consist in dose reductions of administered preparations.

The therapy of non-toxic diffuse goitre, resulting from iodine deficiency, is based on iodine prophylaxis, including an administration of iodine preparations in supplementary doses. In Poland, iodine prophylaxis should currently be applied in pregnant and lactating women with thyroid enlargement, as well as in those without goitre.

Consumption of iodized kitchen salt is not a recommended way of iodine prophylaxis in gestation and lactation, as well as in certain diseases, e.g., in hypertension. In these cases, iodine prophylaxis, based on iodine carrier, such as NaCl, is not an optimal way to supplement the deficit of this element and should rather be replaced by the use of tablets or syrups containing iodine.

At present in Poland, except pregnancy and lactation, as mentioned above, iodine supplementation in diet seems to be practically sufficient, both in children and in adults. Thus, there is no need to use iodine preparations, either in children or in adults, in whom goitre is not diagnosed. In turn, the presence of goitre in children and adults is an indication to use kalium iodide (KI) preparations alone or in combination with L-thyroxine (L-T₄), although, following the present recommendations, in significantly reduced doses, what refers to either preparation.

In case of grade 1 goitre, regardless of patient's age or status predisposing to thyroid enlargement, it is recommended to use iodine preparations only; newborns and children till the age of six should receive – in this case – KI preparation, supplying 25 µg of iodine per day, children in the age of 7–10 years – about 50 µg/day, and older children and adults – up to 100 µg/day. The therapy of grade 2 goitre should include the joint use of KI and L-T₄ preparations, administered in daily doses: up to 50 µg of iodine and 25 µg of L-T₄ – in cases of newborns, infants and children till the age of 6, 50 µg of iodine and 25–50 µg of L-T₄ – in children 7–10 years old and 100 µg of iodine and 50–100 µg of L-T₄ – in older children and adults.

In pregnant and lactating women, it is recommended to administer KI preparations, supplying 100–150 µg of iodine per day – regardless of either goitre occurrence or absence, plus – in addition – L-T₄ preparations in dose of 50 or 100 µg/day in cases of coexisting grade 1 or 2 goitre, respectively.

There is a number of available iodine preparations and multivitamin, iodine-containing preparations. Multivitamin preparations with iodine are recommended

for pregnant women (e.g., Materna, where 1 tablet contains 150 µg of iodine).

The results of studies on adults in Poland, including pregnant women, inhabiting the territories with moderate iodine deficiency, indicate that the joint use of KI and L-T₄ preparations is more effective in the pharmacological management of thyroid enlargement than the administration of each preparation alone [15, 19].

The treatment of iodine deficiency consequences – non-toxic nodular goitre

As already mentioned, non-toxic nodular goitre may be treated pharmacologically or surgically [4]. The pharmacological management is possible only in cases of smaller nodules, with clinical signs of their benign character, following fine-needle aspiration biopsy (FNAB) diagnosis, excluding suspicious and malignant neoplastic lesions. The criterion for the application of pharmacological agents in the therapy of thyroid nodules is their therapeutic efficacy; nodule size reduction has been observed in result of L-T₄ preparations [20, 21, 22], KI preparations or both in combination [21]. The dose of L-T₄ should be determined with respect to TSH concentration levels, which should be maintained below the lower normal value (so called, relative or partial suppression of TSH secretion) [21, 22]. TSH concentrations should not demonstrate values characteristic for overt hyperthyroidism.

It should be emphasized that nodule enlargement observed in the course of treatment with L-T₄ preparation, suggests a process not susceptible to the mechanism of physiological control by the hypothalamus-pituitary-thyroid axis (e.g., malignant neoplastic process), being an indication to surgical intervention [4].

No unequivocal algorithm of management has yet been developed in cases of non-toxic goitre, thus the therapeutic approach has to be individual in each case [4]. This issue is discussed in detail in our subsequent review article in NEL.

Autoimmunologically-induced non-toxic goitre

In the therapy of autoimmunologically-induced non-toxic goitre, a rather careful application of L-T₄ preparations is allowed, with a close monitoring of TSH concentrations and free thyroid hormone levels, as well as of titres of antithyroid antibodies (anti-TPO, anti-Tg, anti-TSHR and – if it is possible – thyroid growth stimulating antibodies), although mere observation is advised by the majority of authors. It should be underlined that L-T₄ reveals usually little therapeutic efficacy. In contrast, the use of iodine preparations, especially in doses bigger from the average prophylactic dose, could – in such cases – contribute to further immunisation and, probably, to thyroid function disorders (iodine-induced hyperthyroidism), what is not recommended.

Positive effects of iodine prophylaxis with respect to goitre prevalence

In the near future, together with the further improvement of iodine status in Poland, even smaller doses of L-thyroxine and KI will be recommended, in comparison with the present values. The first positive results of the iodine prophylactic implementation have been observed in our country, including increased ioduria in adults, decreased goitre incidence in children and a smaller number of cytological diagnoses, such as “follicular neoplasm”, balanced by an increased number of cytological and histopathological diagnoses with better prognosis [23, 24, 25]. It is expected that doses of L-thyroxine and/or KI may be reduced fairly significantly, even twice.

It should be emphasized again that no undesirable side-effects have been observed following administration of prophylactic doses of iodine. Only several times higher doses provide a possibility to reveal iodine-induced hyperthyroidism in genetically predisposed persons or to activate previously non-toxic nodular goitres (i.e., so-called, autonomisation of secretion) [26]. Administration of KI in prophylactic doses to patients with diagnosed autoimmunological disease is not dangerous, however, it does not find any rational justification.

Summing up, grade 1 endemic goitre in children and adults is an indication to apply KI in prophylactic doses, while grade 2 goitre – to joint use of iodine and L-T₄ preparations. Iodine prophylaxis should be applied in gestation and lactation even if no goitre is present. It is certain that, in the near future, the recommendations concerning the therapy of non-toxic goitre, will again be amended, i.e., by decreasing the therapeutic doses of KI and L-T₄ preparations.

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