Abstract

Isotope therapy is one of the methods used in primary hyperthyroidism. The therapy is based on short-range beta radiation emitted from radioactive iodine. Radioiodine administration must always be preceded by pharmacological normalization of thyroid function. Otherwise, post-radiation thyrocyte destruction and thyroid hormones release may lead to hyperthyroidism exacerbation.

Indications for radioiodine therapy in Graves-Basedow disease include recurrent hyperthyroidism after thyrostatic treatment or thyroidectomy and side-effects observed during thyrostatic treatment.

In toxic nodule, isotope therapy is the first choice therapy. Radioiodine is absorbed only in autonomous nodule. Therefore, it destroys only this area and does not damage the remaining thyroid tissue.

In toxic goitre, radioiodine is used mostly in recurrent nodules. Absolute contraindications for radioiodine treatment are pregnancy and lactation. Relative contraindications are thyroid nodules suspected of malignancy and age under 15 years. In patients with thyroid nodules suspected of malignancy, radioiodine treatment may be applied as a preparation for surgery, if thyrostatic drugs are ineffective or contraindicated. In children, radioiodine therapy should be considered in recurrent toxic goitre and when thyrostatic drugs are ineffective.

In patients with Graves-Basedow disease and thyroid-associated orbitopathy, radioiodine treatment may increase the inflammatory process and exacerbate the ophthalmological symptoms. However, thyroid-associated orbitopathy cannot be considered as a contraindication for isotope therapy.

The potential carcinogenic properties of radioiodine, especially associated with tissues with high iodine uptake (thyroid, salivary glands, stomach, intestine, urinary tract, breast), have not been confirmed.

Key words: radioiodine, hyperthyroidism, indications, contraindications, Graves-Basedow disease, toxic goitre, toxic nodule

Introduction

Primary hyperthyroidism is a condition of increased metabolism, thermogenesis, and enhanced sympathetic nervous system activity due to thyroid hormone overproduction (triiodothyronine — T3 and tetraiodothyronine — thyroxine — T4). It affects about 2% of women and 0.2% of men [1].

Etiology of primary hyperthyroidism

Primary hyperthyroidism in young patients (20–40 years old) is mainly due to Graves-Basedow disease [1]. Toxic goitre and autonomous thyroid nodules are the major causes of hyperthyroidism in the elderly and in patients living in iodine deficient areas [1, 2].
Thyroiditis, drug-induced thyroid disorders (amiodarone, interferon-γ), and pregnancy may be connected with hyperthyroidism.

Graves-Basedow disease is an autoimmunological disorder caused by increased level of thyrotropin-receptor antibody (TRAb), which leads to continuous thyrotropin (TSH) receptor stimulation and excessive thyroid hormones production [3]. Clinical manifestations of Graves-Basedow disease are typical for hyperthyroidism. However, cardiovascular abnormalities may be most pronounced in the elderly [4, 5].

Cross reaction between the antigens of the thyroid gland, orbit soft tissue, and eye muscles, as well as fibroblasts and preadipocytes, is responsible for other symptoms of Graves-Basedow disease — thyroid associated orbitopathy, pretibial myxoedema, and acropachy [3].

Toxic goitre (Plummer’s disease) is defined as hyperthyroidism due to thyroid nodules that produce thyroid hormones in excess [6]. Apart from typical hyperthyroid symptoms patients often complain of dysphagia and dyspnoea resulting from pressure in their neck.

Autonomous thyroid nodule (toxic nodule) is a single thyroid nodule releasing thyroid hormones in such high amounts that they suppress thyrotropin production and inhibit the endocrine function of normal thyroid tissue [1]. The disease may be manifested by subclinical or overt hyperthyroidism.

### Diagnosis of primary hyperthyroidism

Ordinarily, typical symptoms suggest hyperthyroidism. However, the diagnosis has to be confirmed by hormonal tests:
- TSH level is reduced or even undetectable;
- free triiodothyronine and tetraiodothyronine (fT₃ and fT₄) concentrations are elevated in overt hyperthyroidism and normal in subclinical thyroid disorders.

Although free thyroid hormones levels reflect the clinical condition of a patient, TSH is usually the first examination that confirms or excludes the suspicion of hyperthyroidism. Nowadays, high accessibility to TSH tests improves the recognition of thyroid disorders.

Antithyroid antibodies (TRAb, antiperoxidase, and antithyroglobulin antibodies) need to be evaluated to assess possible autoimmunological disorders. High TRAb levels determine the diagnosis of Graves-Basedow disease.

Ultrasound examination reveals increased or normal thyroid volume (Graves-Basedow disease) and/or focal lesions (toxic goitre, toxic nodule). In Graves-Basedow disease the echogenicity of thyroid gland is irregular and decreased, which is typical for autoimmunological disorders.

Thyroid scintigraphy in Graves-Basedow disease reveals increased radioisotope absorption in the whole thyroid gland. The co-existence of focal lesions may result in irregular scintigraphic images.

In toxic goitre, hyperactive nodules are shown as regions with high radioiodine absorption (‘hot nodules’). In toxic nodule, the rest of the thyroid gland shows no isotope uptake (Figure 1).

Large goitres may cause pressure on the trachea and/or its dislocation, which can be seen on chest X-ray.

### Treatment

The main therapeutic methods in hyperthyroidism are thyrerotic drugs, radioiodine treatment and surgery.

Thyrotropic drugs (methimazole and propylthiouracil) inhibit thyroid hormone synthesis and release. In monotherapy the initial dose of on thyrostatic drug (methimazole 40–80 mg per day or propylthiouracil 300–400 mg per day) is gradually reduced after 4–6 weeks depending on patient’s clinical and biochemical condition (fT₃, fT₄). Appropriate dosing of thyrostatic drugs requires medical experience. On the one hand, small doses do not reduce the activity of the thyroid gland, and on the other hand, intensive treatment may easily lead to hypothyroidism.

Thyrostatic drugs may be also applied together with L-thyroxine, which supplements the deficit of thyroid hormones. The further schema is contraindicated in pregnancy [7].

Pharmacological treatment should be continued for 18–24 months. Thyroid function has to be regularly controlled during therapy.

### Table 1. Signs and symptoms of hyperthyroidism

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>General</td>
<td>Body weight loss, Increased appetite, Heat intolerance</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>Breathlessness</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Palpitations</td>
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<tr>
<td>Gastrointestinal system</td>
<td>Increased bowel movements</td>
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<tr>
<td>Genitourinary system</td>
<td>Polyuria (rarely), Decreased libido, Women: oligomenorrhea, amenorrhea Men: impotence</td>
</tr>
<tr>
<td>Muscle and skeletal system</td>
<td>Fatigue, Muscle weakness</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Tremor, Nervousness, Agitation, Attention deficit, Insomnia, Psychosis, Disorders of consciousness</td>
</tr>
<tr>
<td>Skin</td>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Tachycardia, Arrhythmias, Hypertension especially systolic blood pressure, Oedema, Heart failure (possible resistance to digoxin)</td>
</tr>
<tr>
<td>Muscle and skeletal system</td>
<td>Muscle atrophy, Acropachy (Graves-Basedow disease)</td>
</tr>
<tr>
<td>Skin, hair, nails</td>
<td>Warm, moist skin (‘velvet skin’), Dermographism, Brittle nails, Fine hair, Pretibial myxoedema (Graves-Basedow disease)</td>
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</tbody>
</table>
Thyrostatic drugs used before radioiodine treatment should be discontinued for 10–14 days before isotope administration to restore appropriate iodine uptake. A similar effect can be obtained when the thyrostatic drug is discontinued 24 hours before radioiodine administration ("bounce effect"). Of note, radioiodine uptake can be considerably decreased in patients who take iodine-containing drugs (amiodarone) or who have received iodinated contrast within 6 months.

Suitable radioiodine dosing can be calculated from a formula referring to thyroid volume, radioiodine uptake, and its half-life time. To assess the efficacy of isotope treatment, we should also determine the radioiodine sensitivity of thyroid tissue. This depends mostly on goitre structure and is individually variable. Since these parameters cannot be estimated it is difficult to predict the effectiveness of radioiodine treatment.

If clinical and biochemical features of hyperthyroidism persist despite radioiodine therapy, thyrostatic drugs can also be given afterwards. To preserve appropriate iodine uptake, pharmacological treatment should begin 4–7 days after radioiodine administration.

While waiting for the effects of the therapy, thyroid function should be controlled regularly. The first control should be performed 6 weeks after treatment. If hyperthyroidism is still observed 4–6 months after isotope administration, the therapy should be repeated. However, in some patients the effects can be observed up to 12 months later [1, 10].

Absolute contraindications for radioiodine treatment are pregnancy and lactation. Relative contraindications are thyroid nodules suspected of malignancy and age under 15 years [1].

In patients with thyroid nodules suspected of malignancy, radioiodine treatment may be applied as a preparation for surgery if thyrostatic drugs are ineffective or contraindicated. In children, radioiodine therapy should be considered in recurrent toxic goitre and in cases of ineffective thyrostatic drugs [1].

The doctor is obliged to ensure that female patients qualified for radioiodine treatment are not pregnant (pregnancy test). Pregnancy should be postponed to approximately six months after isotope administration. By this time, the radioactivity of the isotope should be sufficiently decreased and the function of the thyroid gland should be normalized. Since radioiodine also emits γ radiation, it may influence the development of children, and patients should limit contact with pregnant women and children for approximately two weeks.

Indications for radioiodine therapy in Graves-Basedow disease include recurrent hyperthyroidism after thyrostatic treatment or thyroidectomy, and side-effects of thyrostatic drugs. Since radioiodine therapy is very well tolerated, it is also recommended in patients with concomitant severe diseases.

The first dose of radioiodine is sufficient in 70% of patients with Graves-Basedow disease [1]. The rest require another isotope administration.

In thyroid-associated orbitopathy (TAO), radioiodine treatment may increase the inflammatory process and exacerbate the ophtalmological symptoms. This is due to radiation thyroiditis, which releases thyroid antigens and stimulates antithyroid antibody production. Therefore, in these patients, high doses of radioiodine are recommended to assure complete thyroid tissue destruction, especially when high TRAb levels are observed. The elimination of thyroid antigens and lymphocyte infiltration may
reduce the autoimmunological process that is responsible for hyperthyroidism and TAO.

TAO exacerbation is observed in 15% of patients treated with radioactive iodine, mainly in smokers and patients with high free thyroid hormone levels [1]. However, TAO cannot be considered as a contraindication for isotope therapy. To reduce the risk of TAO exacerbation, the patient should be given glucocorticosteroids. The treatment starts the day after radioactive iodine administration. The initial dose of prednisone (0.4–0.5 mg/kg mc. bw/d.) is gradually reduced during 6–9 weeks. Nevertheless, such therapy does not protect all patients from TAO development.

In toxic goitre, radioactive iodine is used mostly in recurrent goitre. Isotope therapy reduces thyroid volume by approximately 40% [10]. When a patient does not respond to radioactive iodine therapy, another isotope administration or surgery needs to be considered. The efficiency of isotope therapy is estimated at 70% [10]. Fine-needle biopsy should always be performed to exclude malignancy in the thyroid gland.

Since iodine uptake in toxic goitre is lower than in Graves-Basedow disease, the doses of radioactive iodine need to be higher. There are studies evaluating the use of recombinant TSH to increase iodine uptake in these patients [11]. In the past, large multinodular goitres that pressed and dislocated the trachea were considered as contraindications for radioactive iodine treatment. It was believed that oedemas associated with radiation thyroiditis might additionally reduce airflow and aggravate dyspnoea. However, such concerns are groundless.

In toxic nodules, isotope therapy is the first choice therapy. Radioiodine is absorbed only in autonomous nodules. Therefore, it destroys only this area and does not damage the remaining thyroid tissue. Hypothyroidism develops in 10–30% of patients treated with radioactive iodine, especially due to Graves-Basedow disease [1]. However, it cannot be considered as a side-effect of such therapy. It is assumed that radioactive iodine treatment leads to hypothyroidism in most patients. Its occurrence is estimated at 1–2% per year [1]. In toxic nodules, focused isotope absorption results in selective destruction of autonomous area. Low TSH levels decrease iodine uptake in surrounding tissue, which additionally protects healthy thyroid. Therefore, the effectiveness of radioactive iodine treatment in toxic nodules is very high and the risk of hypothyroidism is slow.

Isotope therapy is usually well tolerated. Severe radiation thyroiditis with pain radiating to the jaw and ears is very rare. Post-radiation hyperthyroidism predominantly results from insufficient thyrostatic preparation before isotope administration or from extensive tissue destruction and increased thyroid hormone release. Non-steroidal anti-inflammatory drugs reduce the symptoms.

Iodine is highly soluble in water. Patients treated with radioactive iodine are recommended to drink more fluids for better iodine excretion.

The potential carcinogenic properties of radioactive iodine, especially associated with tissues with high iodine uptake (thyroid, salivary glands, stomach, intestine, urinary tract, breast), have not been confirmed [12]. Surgery is recommended mainly in Graves-Basedow disease and toxic goitre. The advantages of surgical treatment are very high effectiveness and the possibility of histopathological evaluation.

In Graves-Basedow disease, total thyroidecctomy is preferred to assure complete thyroid excision and elimination of thyroid antigens.

In toxic goitre, surgery is indicated in large goitres pressing on surrounding tissues as well as in thyroid nodules suspected of malignancy [1]. In these cases total thyroidecctomy should be performed.

References