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Hypothyroidism and Radioiodine Therapy

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1. Introduction

Thyroid diseases are the most common endocrinopathies. In the Czech Republic they make up 80 to 90% workload of the endocrine centers. Thyroid diseases requiring treatment or at least follow up affect at least 5% of our population, for women middle-aged and older 10 to 15%.

In some thyroid diseases radioiodine ^{131}I has been used for treatment.

Hypothyroidism arises most often in the Czech Republic on the basis of chronic autoimmune thyroiditis, hypothyroidism is relatively common as artificial - after surgical or radioiodine therapy (RAIT) of various diseases of the thyroid gland.

2. Hyperthyroidism

In hyperthyroidism three major treatment modalities are currently available: antithyroid drugs, radioiodine and surgery, each of which presents advantages and restrictions (Surk et al.,1990). RAIT is considered as the most comfortable and economical approach of hyperthyroidism treatment caused by Graves´ disease or toxic nodular goiter. Such treatment is indicated in patients with/or without functional autonomy to normalize thyroid function, and to reduce thyroid volume (Meier et al., 2002).

The therapeutic use of radioiodine to treat hyperthyroidism from Grave's disease was first reported by Saul Hertz in 1941. Hertz administered produced a I-130 - I-131 mixture as a therapeutic dose to the first human patient with Graves' disease at Massachusetts General Hospital. This was the first successful treatment of humans with an artificially produced radioactive material. Gradually a series of 29 patients were treated and documented (http://en.wikipedia.org/wiki/Saul_Hertz#cite_note-10). The Journal of the American Medical Association published in May 1946 the paper with results of a five year follow up study of the 29 patients and documented the successful treatment and safety of radioactive iodine for the treatment of hyperthyroidism. The follow-up study firmly launched the use of RAIT as a standard treatment for Graves´ disease (Hertz & Roberts, 1946).

RAIT is applied mostly in hyperthyroid adults. However, it has recently gained appreciation also in children (Brown, 2009). In children radioiodine treatment should be considered in recurrent toxic goiter and in cases of ineffective thyrostatic drugs (Cooper, 2003). RAIT of

Graves' disease was introduced 70 years ago, and it is estimated that more than one million individuals have been treated with ^{131}I for hyperthyroidism (Chapman, 1983). The use of radioactive iodine has been detailed for more than 1200 children (Rivkees et al., 1998). Patients as young as 1 yr of age have been treated with ^{131}I with excellent outcomes (Rivkees et al.1998). Some studies have reported remission rates that exceed 95%, with very rare complications (Levy et al., 1988, Read et al., 2004, Rivkees et al.1998). Properly administered radioactive iodine remains an ideal form of treatment for Graves' disease in the pediatric population and it is an effective cure for Graves' disease which is associated with few acute side effects (Rivkees & Dinauer 2007). When radioiodine is used at appropriate doses, there is a very high cure rate without increased risks of thyroid cancer or genetic damage (Rivkees, 2001). Also data of Moll & Patel (Moll & Patel, 1997) from nearly 8 years experience with ^{131}I therapy support consideration of RAIT within 3 to 6 months of diagnosis of pediatric Graves´ disease as an effective, efficient, and probably safe alternative approach to the traditional antithyroid therapy of Graves´ disease in children.

For 70 years radioidine has been used to treat most cases of Graves´ disease and thyroid autonomies. The thyroid gland utilizes iodine for the synthesis of thyroid hormones. The cells do not differentiate between stable and radioactive iodine. If radioactive iodine is administered, it is trapped and then organified by thyroid follicular cells like nonradioactive iodine. The therapeutic effects of ^{131}I sodium iodide are due to the emission of ionizing radiation from the decaying radionuclide. The therapy is based on short-range beta radiation from radioactive ^{131}I. The beta particles, due to their high mean energy (190 keV, with typical beta-decay spectra present) have a tissue penetration of 0.6 to 2 mm (Skugor, 2006). Radioiodine administration should be preceded by pharmacological normalization of fT4 and fT3 levels, beacause post-radiation thyrocyte destruction and thyroid hormone release can lead to hyperthyroidism exacerbation (Gurgul & Sowinski, 2011). In some cases it is possible to withdraw antithyroid drugs 10-14 days before radioiodine administration to restore appropiate iodine uptake. It is known that one of the cause of reduced ^{131}I uptake and shortened effective half life is pre-treatment with antithyroid drugs (ATD), which may have an additional radio-protective effect. It can influence the outcome of ^{131}I therapy (Sabri et al., 2001, Walter et al., 2002) with possibility a risk of treatment failure for lower delivered radioiodine doses to the target tissue (Dunkelmann et al., 2005). Tuttle et al. describe that antithyroid drug therapy has been associated with relative radioresistance and with a decrease in radioiodine therapy effectiveness (Tuttle et al., 1995). A similar effect as longer discontinuation of ATD (10-14 days) can be obtained when ATD is discontinued 24 hours before ^{131}I administration („bounce effect") (Gurgul & Sowinski, 2011). But in severe hyperthyreoidism it is not possible to withdraw ATD for a long time, that is why discontinuation of ATD starting two or three days before ^{131}I is now widely accepted (Walter et al., 2002). 2-day ATD withdrawal prior to radioiodine administration sufficiently increases the radioiodine uptake and does not exacerbate hyperthyroidism compared to 7-day withdrawal in Graves´ disease patients. There is not significant diference in RAIT outcomes between 2-day and 7-day groups. In order to prevent serum thyroid hormone increase after ATD withdrawal and RAIT, a 2-day ATD withdrawal period before RAIT may be useful for high-risk patients such as the elderly and patients with cardiac complications (Kubota et al., 2006). Pretreatment with propylthiouracil but not methimazole, discontinued even 15 days before radioiodine administration, reduces the rate of success of ^{131}I therapy. Propylthiouracil pretreatment and large goiters are related to failure of radioiodine therapy.

Propylthiouracil should be avoided if radioiodine is considered in the management of hyperthyroid patients with Graves´ disease (Santos et al., 2004). Bonnema et al. (Bonnema et al., 2004) have shown, in a randomized set-up, that propylthiouracil treatment before ^{131}I therapy for hyperthyroid diseases approximately halves the cure rate at 1 year and that after classification the outcome into two categories, cured (euthyroidism or hypothyroidism) or not cured (recurrence), the treatment failure rate in patients with toxic nodular goiter was approximately 4 times as high in the propylthiouracil pretreatment group as in the group without propylthiouracil pretreatment, whereas the diference among patients with Graves' disease was less obvious. Andrade et al. have demonstrated that thyroid hormone levels stabilize or decrease after RAIT in patients with Graves' hyperthyroidism who are not pretreated with ATD (Andrade et al., 1999). Andrade et al. proved that short term increase in thyroid hormone levels in patients with Graves' hyperthyroidism receiving RAIT occurs mainly as a result of discontinuing antithyroid drug therapy. Among patients who received RAIT without pretreatment, serum thyroid hormone levels did not change or decreased in the 30-day interval after radioiodine administration. They postulated that RAIT without pretreatment with ATD can be safely prescribed (Andrade et al., 1999). Burch et al. (Burch et al., 2001) concluded that pretreatment with ATD does not protect against worsening thyrotoxicosis after radioiodine, but this pretreatment provides a measure of protection by establishing lower baseline values should an exacerbation of thyrotoxicosis occur. The findings support the recommendation that most patients with Graves' disease do not require antithyroid drug pretreatment before receiving radioiodine.

In benign conditions such as Graves´ disease, division of some metabolically active cells is prevented by the effect of the ionizing radiation of radioiodine. Cell death is another mechanism activated when the cells are exposed to high levels of radiation, for example in autonomous adenoma, where the suppressed normal thyroid tissue is essentially spared with delivery of a very high concentration to the cells of the autonomous adenoma (toxic nodule). Cell death is followed by replacement with connective tissue, which may lead to hypothyroidism, depending on the number of cells destroyed and replaced by fibrous nonfunctioning tissue. Since 90% of the radiation effects of ^{131}I are due to beta radiation, which has a short range in tissue, the extrathyroid radiation, and consequently the side effects, are minimal.

The potential risk after radioiodine therapy of hyperthyroidism that is most extensively discussed in the literature is cancer induction (Lacko et al., 2001, Reiners, 1997, Vlček & Neumann, 2002). Since the 1980s, large-scale, long-term (15–17 years) follow-up studies of cancer risk in patients treated with radioiodine for hyperthyroidism have been reported (Franklyn et al., 1999, Goldman et al., 1988, Hoffman et al., 1982, Holm et al., 1991) with conflicting results. The first 2 longterm studies were continuations of the Cooperative Thyrotoxicosis Therapy Follow-up Study (Hoffman et al., 1982, Goldman et al., 1988). Hoffman et al. (Hoffman et al., 1982) reported no difference between 1005 women treated with radioactive iodine and 2141 women treated with surgery for hyperthyroidism in total cancer incidence, breast cancer, or leukemia. Although based on a small number of cases, an elevated risk of cancer was observed in the thyroid gland and other organs that concentrate radioiodine (salivary glands, digestive tract, kidney, and bladder) (Hoffman et al., 1982). In a study of Goldman et al. (Goldman et al., 1988) the cancer incidence of 1762 hyperthyroid women (80% treated with radioactive iodine) did not differ from that

of US white women. In a large population-based study of 10552 Swedish patients who received RAIT for hyperthyroidism, significantly elevated overall cancer incidence was observed compared with the Swedish population (Holm et al., 1991). Among 10-year survivors, significantly elevated risks were seen for cancers of the stomach, brain, and kidney (Holm et al., 1991). In a population-based study of 7417 patients treated with radioiodine for hyperthyroidism in Birmingham (UK), the overall cancer incidence and mortality decreased, but the incidence and mortality of cancers of the small bowel and the thyroid gland were increased compared with expected rates (Franklyn et al., 1999). According to the American Cooperative Thyrotoxicosis Therapy Follow-up Study (Ron et al., 1998) RAIT of hyperthyroidism was linked to a slightly increased risk for thyroid cancer. Metso proved that cancer incidence, especially cancer of the stomach, kidney, and breast, was higher in patients treated with radioiodine for hyperthyroidism (Metso et al., 2007). On the other hand, a Swedish follow-up study did not reveal any increased risk of thyroid cancer (Holm et al., 1991). Although radioactive iodine is being used in progressively younger ages, it is not known if there is an age below which high-dose ^{131}I therapy should be avoided. Risks of thyroid cancer after external irradiation are highest in children younger than 5 yr of age and progressively decline with advancing age (Boice, 1998, 2006, Dolphin, 1968, Read et al., 2004). If there is residual thyroid tissue in young children after RAIT, there is a theoretical risk of thyroid cancer. It may therefore be prudent to avoid RAIT in children younger than 5 years (Rivkees & Dinauer, 2007). In addition to thyroid cancer, potential influences of ^{131}I therapy on other cancers need to be considered. Follow-up from the large cohort of the Cooperative Thyrotoxicosis Therapy Follow-Up Study did not find increased risks of leukemia in the ^{131}I -treated group, as compared with the drug- and surgery-treated groups (Saenger et al., 1968). No increase in overall cancer mortality was seen in the ^{131}I-treated patients either (Ron et al., 1998). In one other study, excess thyroid cancer mortality after ^{131}I therapy for Graves' disease was observed during early, but not late, follow-up (Hall et al., 1992a). Yet this was related to increased cancer surveillance and detection, not ^{131}I effects (Hall et al., 1992a). Edmonds and Smith (Edmonds & Smith, 1986) reported a small but significant excess of incidence and mortality of leukemia in 258 patients treated with high-activity radioiodine for thyroid cancer (2960 MBq to 5550 MBq). However, no increased risk for malignancies of the hematopoietic system was found in the study of Metso et al. (Metso et al., 2007), which is in the agreement with earlier studies on patients treated with radioactive iodine (370 MBq to 555 MBq) for hyperthyroidism (Franklyn et al., 1999, Hall et al., 1992b, Hoffman et al., 1982, Holm et al., 1991). No increase in the risk of thyroid malignancies has been observed in patients treated with radioiodine for hyperthyroidism in most of the published long-term follow-up studies (Augusti et al., 2000, Goldman et al., 1988, Holm et al., 1991).

Several factors affect the therapeutic activity to be administered to patients suffering from hyperthyroidism including factors related to gland itself, particularly its size, the level of radioiodine uptake, the rate of iodine turnover in the gland (measured by the effective half-life), scintigraphic findings of uniform or nonuniform uptake, and whether nodules are present. The dose (in Gray) is dependent on how the nuclear medicine physician defines the goals of therapy. If the control of hyperthyroidism is the most important consideration, the total activity (in megabecquerels - MBq) or the dose per gram of estimated thyroid tissue

weight will be higher than when the physician is trying to avoid or delay hypothyroidism. In our department we use individually calculated therapeutic radioiodine activity (in MBq) using Marinelli´s formula (Marinelli et al., 1948):

$$\text{Activity} = K * \frac{\text{Absorbed Dose} * \text{Volume}}{\text{Max. Uptake (\%)} * \text{eff. Half - life}}$$

K = 24,94; absorbed dose in Gray-Gy; volume of target thyroid tissue in ml or weight in g; effective half time in days

We calculate it from a formula referring to thyroid volume, radioiodine uptake and its half-life time. But it is difficult to determine the radioiodine sensitivity of thyroid tissue which depends on the structure of normal sized thyroid or goiter and is individually variable. This parameter cannot be estimated and that is why it is difficult to predict the effectiveness of RAIT. While waiting for the effects of the RAIT, thyroid function should be controlled regularly. If hyperthyreoidism is still present 4-6 months after ^{131}I administration, the therapy can be repeated. However, in some patients the therapeutic effects can be observed up to 12 months later (Cooper, 2003, Gurgul & Sowinski, 2011, Nygaard et al., 1999b). In our opinion calculated radioiodine activity is advantageous and we prefer it in RAIT, but some authors prefer fixed activities (Leslie et al., 2003).

2.1 Graves´ disease

Thyroid scintigraphy shows uniform uptake throughout thyroid gland (Fig. 1) or varying degrees of nonuniform uptake.

This nonuniformity is related predominantly to different stages of involution of the disease with variable amounts of fibrosis based on the duration of the disease. Infiltration of extraocular muscles by an inflammatory reaction consisting predominantly of lymphocytes is the main pathological feature of ophtalmopathy. These lymphocytes are sensitized to antigens common to the orbital muscles and thyroid gland.

Indications for RAIT include recurrent hyperthyroidism after thyrostatic treatment or thyroidectomy. It is also recommended in patients with concomitant severe diseases (Gurgul & Sowinski, 2011). The first activity of ^{131}I is sufficient in 70% of patients with Graves´ disease (Cooper, 2003). The rest requires repeated RAIT.

Absolute contraindications to ^{131}I therapy is pregnancy and breastfeeding (Sisson et al., 2011).

Although there is general consensus that radioiodine is a safe and effective treatment for Graves' hyperthyroidism, debate remains in terms of the optimal method for calculating the activity (in MBq) and even what the criteria should be for defining optimal. Sustained euthyroidism would clearly be the most desirable outcome, but this appears to be a futile objective, because high rates of cumulative hypothyroidism are reported in most series.

Findings of Leslie et al. (Leslie et al., 2003) confirm this result, with the vast majority developing permanent hypothyroidism and very few with euthyroidism. Therefore, the objective of eradicating hyperthyroidism at the lowest effective radioiodine dose may well

be the preferred strategy. This has led some groups to suggest a larger initial radioiodine dose (in Gy) and activity (in MBq) to minimize the need for retreatment and the morbidity and medical costs associated with ineffective primary treatment. Alternatively, others favor a low activity approach (185 MBq), at least for those with mild disease and without complications (Nordyke & Gilbert, 1991). Allahabadia et al. (Allahabadia et al., 2001), who use fixed therapetic activity reported these results: patients given a single activity of 370 MBq had a higher cure rate than those given 185 MBq, but an increase in hypothyroidism incidence at 1 year. There was no difference in cure rate between the groups with Graves' disease and those with toxic nodular goiter, but Graves' patients had a higher incidence of hypothyroidism. Males had a lower cure rate than females, whereas younger patients (<40 years) had a lower cure rate than patients over 40 years old (Allahabadia et al., 2001).

Fig. 1. Thyroid scintigraphy – diffuse goiter in Graves´ disease

2.2 Toxic nodular goiter (Plummer´s disease)

It means hyperthyroidism in glands with both single and multiple toxic nodules. The toxic nodular goiter contains nodules that are not hyperactive.

Therapy of Graves´ disease and toxic nodular goiter can be conservative with drugs, surgical and by radioiodine. Surgery is connected with higher risk, RAIT is indicated most often. RAIT in the world today is the most common and the least expensive therapy. It is indicated mainly for failure of conservative treatment, also in the organ complications, especially circulation (atrial fibrillation, circulatory failure), or where the operation is

contraindicated for other reasons. In toxic nodular goiter radioiodine is used mostly in recurrent goiter. This therapy reduces thyroid volume by approximately 40%. The efficiency of RAIT is estimated at 70% (Nygaard et al., 1999b).

Late complication after radioiodine therapy is the development of transient or permanent hypothyroidism. The early transient hypothyroidism is that which arose within six months of treatment with radioiodine. It is a block of hormonogenesis after radioiodine. It is caused by an immunological mechanism.

As the early permanent hypothyroidism we consider a steady increase of TSH levels within 1 year after therapeutic application of radioiodine. In the permanent hypothyroidism the failure of hormonogenesis is involved in addition to immunological processes, damage of the follicular cell nuclei, which leads to accelerated aging and cell death. Hypothyroidism develops after radioiodine therapy like postoperatively in patients with hyperthyroidism. Hypothyroidism after RAIT gradually increases with time, several years after this therapy. It is detected at several tens of percent of such treated patients. Hypothyroidism develops in 10-30% of patients treated with radioiodine, especially due to Graves´ disease (Cooper, 2003). However, it cannot be considered as a side-effect of such therapy. Hypothyroidism ocurrence is estimated at 1-2% per year (Cooper, 2003). Despite the numerous attempts to design dosage schedules aiming at euthyroidism, hypothyroidism occurs in the majority of patients throughout life (Pauwels et al., 2000).

Hypothyroidism occurs at a linear rate on a permanent basis (Staffurth, 1987, Taylor et al., 1984). Besides permanent hypothyroidism, transient hypothyroidism may be seen in patients 2-5 months (or in the first year) after RAIT with spontaneous recovery in the following months (Connell et al., 1983, Dorfman et al., 1977).

^{131}I activities are typically calculated to deliver the desired amount of radiation based on gland size and radioactive iodine uptake (Quimby et al., 1970). Some centers administer to all patients the same fixed activity of ^{131}I with excellent outcome (Nebesio et al., 2002). When children are treated with the dose more than 200–250 Gy/g, hypothyroidism is achieved in nearly 95% of patients (Rivkees & Cornelius, 2003). But in our opinion these doses per gram are too high. Gland size also influences treatment outcome, as higher doses of ^{131}I are needed to induce hypothyroidism when large glands are present (up to 60 g) (Rivkees & Cornelius, 2003). When thyroid size exceeds 80 g, remission rates after ^{131}I therapy are poor (Peters et al., 1996). Thus, surgery is preferred when thyroid gland size is large (>60–80 g). Hamburger reported the largest series of pediatric patients with Graves´ disease in which ^{131}I therapy resulted in relatively uncomplicated clinical courses, except for hypothyroidism requiring lifelong thyroid hormone replacement in 89% (Hamburger, 1985).

Several studies have attempted to determine the optimal activity of radioiodine for curing hyperthyroidism, while avoiding the development of permanent hypothyroidism. Regimens used have included low activity 80 MBq (Franklyn et al., 1991, Lowdell et al., 1985, Nordyke & Gilbert 1991), various fixed activity (185, 370, and 555 MBq) (Franklyn et al., 1991, Jarlov et al., 1995, Nordyke & Gilbert, 1991, Watson et al., 1988), and activities calculated on the basis of thyroid size, the uptake of radioiodine, or the turnover of radioiodine (Franklyn et al., 1991, Jarlov et al., 1995, Sridama et al., 1984). Most dosimetric methods have the benefit of including a measure of thyroid size in their formulas, thereby administering a dose of radioiodine proportional to size of the gland and theoretically

increasing the probability of cure, because this has been considered to be an important prognostic factor for success after RAIT. In addition, the use of isotope uptake measurements, as part of the activity calculation protocol, can confirm the absence of thyroiditis and identify patients with values at the extreme ends of the reference range of isotope uptake or turnover, which may predict failure of RAIT (Kaplan et al., 1998). Despite these potential benefits of calculated acitivities, several studies have failed to demonstrate improvements in cure rate over fixed activities (Catargi et al., 1999, Jarlov et al., 1995, Peters et al., 1995). Furthermore, there is little evidence that using a calculated activity has any advantage over a fixed-activity regimen, in terms of preventing hypothyroidism (Turner et al., 1985, Sridama et al., 1984), so many centers and clinicians prefer the use of a fixed-activity regimen (Hedley et al., 1992, Franklyn, 1994).

Although low fixed activities (185 MBq) are associated with a reduced early incidence of hypothyroidism, they often result in unacceptably low cure rates. Moreover, the development of long-term hypothyroidism seems to be inevitable, irrespective of the amount of radioiodine administered, with an annual incidence of 2–3% many years after therapy (Franklyn et al., 1991, Hennemann et al., 1986). Some clinicians now prefer to give a large ablative activity (555 MBq and upwards), which results in early hypothyroidism, so that the need for long-term follow-up of thyroid function in euthyroid patients is obviated.

2.3 Endocrine orbitopathy

Very advanced endocrine orbitopathy has a significant symptomatology. Therapy of endocrine orbitopathy complicated thyreotoxicosis is done with the cooperation with ocularist. RAIT 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 ^{131}I are recommended to assure complete thyroid tissue destruction, especially when high thyroid stimulating hormone receptor antibody (TRAb) levels are observed. The elimination of thyroid antigens and lymphocytes infiltration may reduce the autoimmunological process that is responsible for hyperthyroidism and endocrine orbitopathy (Gurgul & Sowinski, 2011). After calming of thyrotoxicosis we must think of definitive therapy - thyroidectomy followed by ablative radioiodine therapy. Of course then the patient is without the thyroid gland, with rapid development of hypothyroidism. The hormonal replacement therapy is necessary.

2.4 Thyroid autonomies

Autonomously functioning thyroid tissue is characterized by the ability to function without TSH. Neither the antibodies nor TSH is involved. The group of follicular cells just continues autonomously to produce excess amount of thyroid hormones. For clinical diagnosis, radioiodine or ^{99m}Tc-pertechnetate imaging of the thyroid gland is performed. Normally the scan would show increased radionuclide uptake by the autonomous thyroid area (with or without nodule) compared with surrounding normal thyroid tissue. Histological examinations of tissue corresponding to scintigraphically autonomous areas show different architectural patterns and histological features of follicular cells compared with normal quiescent tissue (Kraft, 2006).

The main cause of functional autonomies of the thyroid is iodine deficiency. A higher prevalence of functional autonomies in thyroid tissue have been described in areas with an endemic iodine deficiency (Belfore et al., 1983, Guglmann et al., 1995), the prevalence in countries replete with iodine is below (Hamburger, 1980).

The main pathologic attribute of thyroid functional autonomies is the loss of regulation in the axis of hypothalamus-hypophysis-thyroid.

The histopathology of goiter varies with etiology and age of the goiter. Initially, uniform follicular epithelial hyperplasia (diffuse goiter) is present with an increase in thyroid mass. As the disorder persists, the thyroid architecture loses uniformity, with the development of areas of involution and fibrosis interspersed with areas of focal hyperplasia. This process results in multiple nodules. On scintigraphy, some nodules are "hot," with a high radionuclide uptake (in the end autonomous), or "cold," with a low radionuclide uptake, compared with the normal thyroid tissue. The development of nodules correlates with the progression of functional autonomy and a reduction in TSH levels. Clinically, the natural history of a nontoxic goiter is growth, nodule production, and functional autonomy, resulting in thyrotoxicosis in a minority of patients (Lee & Ananthakrishnan http://www.emedicine.com/med/TOPIC919).

Functional autonomous tissue can present as an autonomous adenoma with nodule (Fig. 2), multifocal functional autonomy in multinodular goiter (MFA) (Fig. 3), or unifocal functional autonomy in thyroid glands without nodules (UFA) or diffuse functional autonomy (DFA).

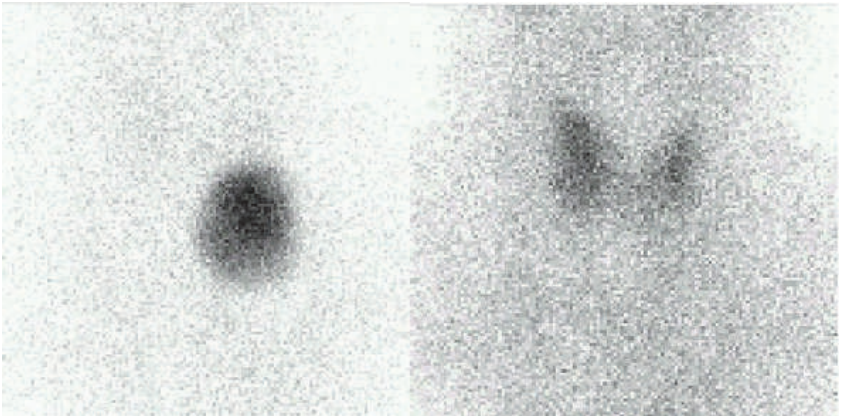

Fig. 2. Thyroid scintigraphy - autonomous adenoma before (on the left) and after (on the right) successful RAIT

Thyroid adenomas (and most nodules in goiters), even if morphologically heterogenous, are true benign tumors (Studer & Derwahl, 1995).

For the diagnostics of thyroid fuctional autonomy and the evaluation of the radioiodine therapeutic effect of functional autonomies, a thyroid scintigraphy is the basic and necessary procedure. Decisions concerning the definitive treatment of thyroid autonomy should take into account previous episodes of hyperthyroidism, objective parameters of risk

stratification in euthyroid patients, concomitant diseases, and the probability of future iodine exposure.

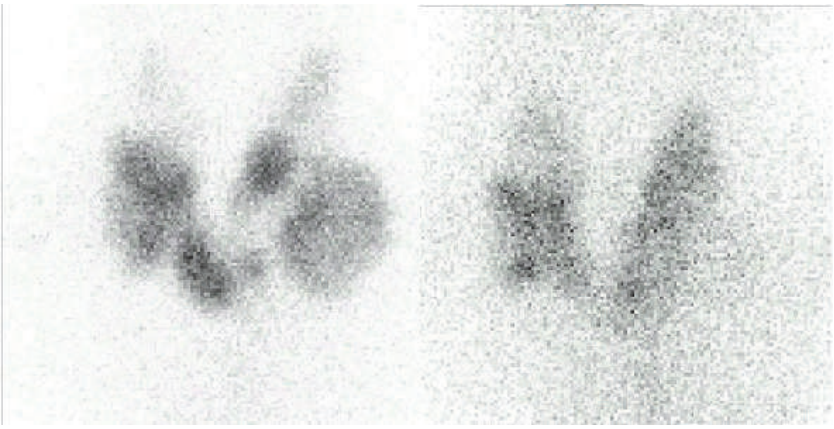

Fig. 3. Thyroid scintigraphy - multifocal functional autonomy in multinodular goiter before (on the left) and after (on the right) successful RAIT

Autonomous adenoma in single thyroid nodule or unifocal or multifocal thyroid autonomies can secrete sufficient thyroid hormones to cause hyperthyroidism. In autonomous adenoma palpable nodule can suppress paranodular tissue (decompensated adenoma) with suppressed TSH with normal or higher fT3 and/or fT4 or the function of the surrounding tissue is preserved (compensated adenoma). Initial thyreosuppressive conservative therapy cannot have permanent effect and we cannot expect remission and it should be treated with radioiodine or operate.

Patients with autonomy who develop hyperthyroidism spontaneously or after iodine excess carry a high risk of recurrence, ranging from 55% up to 81% (Voth et al., 1990). There is general agreement that if hyperthyroidism occurs or has occurred in autonomy, definitive treatment is indicated. RAIT is indicated in patients with functionally relevant autonomy to normalize thyroid function, to remove functional autonomy, and to reduce thyroid volume (Meier et al., 2002).

Radioiodine treatment should be preferred over surgery in patients with smaller goiters (volume <100 ml), the absence of cold nodules or cysts, or the lack of suspicion for malignancy, as well as in those who have undergone previous surgery or would be at increased risk from a surgical intervention. On the other hand, surgery should be preferred in all patients who do not meet these criteria, as well as in the presence of compression symptoms and when there is a need for an immediate therapeutic effect. The risk of relapse on medical treatment with ATD alone is very high, exceeding 80% and long-term antithyroid treatment is not safe in elderly patients, mainly because of poor compliance or a dose reduction by inexperienced physicians. Ablative treatment should be preferred in patients with overt hyperthyroidism owing to functional autonomy. RAIT represents the most comfortable and economic approach (cost of radioiodine and short hospitalization is lower than surgery or long-term conservative therapy). The aim of RAIT in autonomy is the

destruction of autonomous tissue with restoration of euthyroidism. Some groups have successfully used standard activities without any activity calculation. We advocate individual pretherapeutic dosimetry to determine the activity necessary to achieve a targeted radiation dose in autonomously functioning tissue. If the elimination of hyperthyroidism in patients with autonomy is achieved, RAIT can be considered successful. The normalization of serum TSH has been proposed as a criterion in the evaluation of a post-therapeutic outcome. Serum TSH >0,5 mU/l excludes autonomous thyroid function with a probability of 88% in an iodine deficiency area (Becker et al., 1992). Therefore, the normalization of this parameter following radionuclide treatment usually indicates a favorable result. Long-term suppressed serum TSH after ^{131}I, on the other hand, has a low predictive potential, as it is often decreased for a prolonged period, despite therapeutic success (Seeger et al., 1995).

In our great group of 868 patients with unifocal and multifocal functional autonomy, and disseminated functional autonomy who received at least one treatment of radioiodine side-effects were minimal. Postradiation hypothyroidism was diagnosed in 38 patients (4,4%). Such a low incidence of hypothyroidism can be influenced by these factors: 1. A very low number of patients had previous treatment with methimazole, which is associated with a faster progression toward hypothyroidism (Ceccarelli et al., 2005); 2. Before ^{131}I therapy in patients with functional autonomy, the degree of nonautonomous thyroid tissue suppression was high, and this tissue was not influenced by radioiodine beta rays (radioiodine is absorbed only in autonomous nodule or tissue, therefore it destroys only this area and does not damage the remaining thyroid tissue); 3. follow-up of our patients was 2 years long, and certainly later, the number of hypothyroid patients can (but maybe not) increase (Ceccarelli et al., 2005). In the literature, the incidence of hypothyrodism after RAIT for functional autonomy of the thyroid is described in 10%–20% cases (Reiners & Schneider, 2002) and even in 60% (Ceccarelli et al., 2005). 4. pretherapeutic dosimetry with a treatment by means of individually calculated ^{131}I activity (Kraft & Stepien, 2007). Generally, in thyroid autonomies, focused radioiodine absorption only or almost only in autonomous areas results in selective destruction of these areas. Low TSH levels decreases radioiodine uptake in surrounding tissue, which additionally protects healthy thyroidal tissue. Therefore, the effectiveness of RAIT in thyroid autonomies is very high and the risk of hypothyroidism is low (Gurgul & Sowinski, 2011). This is in contrast to the situation for example in RAIT of Graves´ disease and toxic nodular goiter. Non-suppressed serum TSH before ^{131}I therapy has been mentioned as a risk factor for development of hypothyroidism (Farrari et al., 1996). Nygaard (Nygaard et al., 1999a) had a cure-rate of 75% within 3 months when treating autonomous solitary thyroid nodules with ^{131}I in 62 patients. The thyroid volume was reduced by 35% within 3 months and 45% after 2 years. Side effects were few and consist of hypothyroidism in 8% with a median follow-up of 5 years (Nygaard et al., 1999a).

3. Euthyroid goiter

Small eufunctional goiter usually does not carry any trouble. The growth of goiter gradually creates local problems and in advanced stages we can objectively find the compression of the trachea and esophagus, abnormal innervation of the larynx, possibly obturation of the upper aperture. On scintigraphy the diffuse goiter accumulates homogeneously, in nodular goiter some areas accumulate with reduced and often with increased activity (Fig.4).

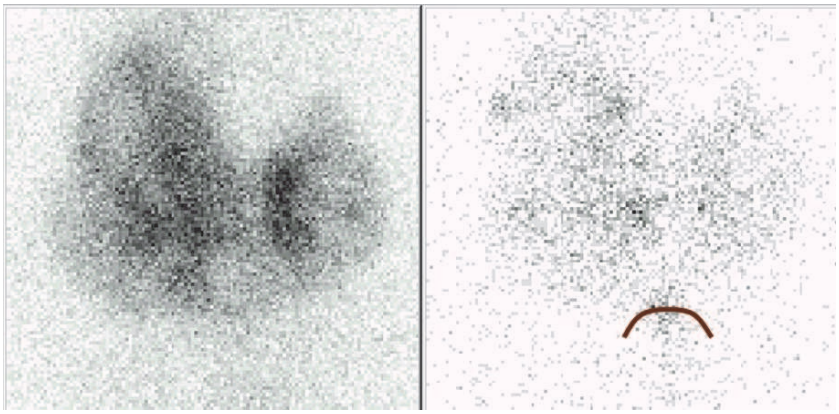

Fig. 4. Thyroid scintigraphy – nodular goiter with normal function and mechanical syndrome

Goiter with mechanical syndrome is a disease that has to be solved urgently and radically (Fig.5). In the first place surgery comes. If thyroidectomy is contraindicated, the use of RAIT is appropriate.

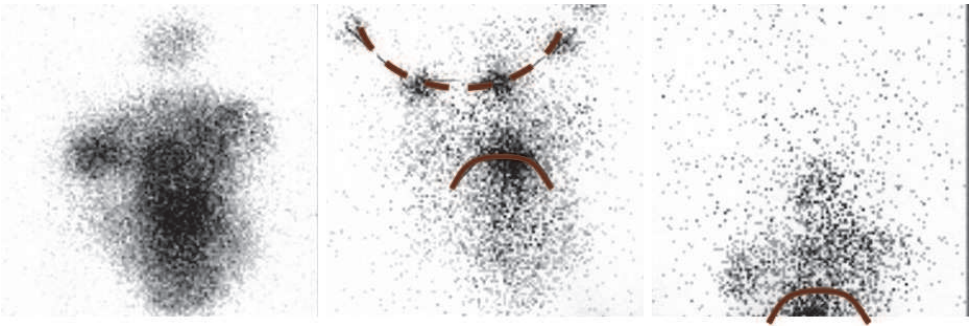

Fig. 5. Thyroid scintigraphy – retrostrernal goiter after thyroidectomy with mechanical syndrome

After this treatment, postradiation hypothyroidism is a common finding with need to use replacement therapy of thyroid hormones.

4. Differentiated Thyroid Cancers (DTC)

Radioiodine is the mainstay of therapy for residual, recurrent, and metastatic thyroid cancer that takes up iodine and cannot be resected. About 90% or more of thyroid carcinomas are well differentiated (papillary or follicular types), which take up iodine and accordingly can be successfully treated with ^{131}I. The therapeutic effects on differentiated thyroid cancer is based on destruction of cells by high dose of administered radioiodine. RAIT is defined as the systemic administration of ^{131}I - sodium or potassium iodide for selective irradiation of thyroid remnants, microscopic DTC or other nonresectable or incompletely resectable DTC,

or both purposes. Based on the primary goal of the RAIT, there are two main forms of the procedure (Luster et al., 2008). The first form, radioiodine ablation, is a post-surgical adjuvant modality. It seeks to eliminate thyroid remnants to increase the sensitivity and specificity of follow-up testing for DTC persistence or recurrence, namely, of assays of serum thyroglobulin (Tg) as a tumour marker and of diagnostic whole-body scintigraphy (dxWBS) (Fig. 6). Ablation also allows sensitive "post-therapy" whole-body scintigraphy (rxWBS) (Fig. 7) that may detect previously occult metastases (Dietlein et al., 2007) and serves to treat any microscopic tumour deposits.

Ablation, therefore, may reduce long-term morbidity and possibly, mortality (Dietlein et al., 2007, Sawka et al., 2004, Pacini et al., 2005). Ablation success is evaluated 6–12 months after the ablation procedure. The second form of RAIT, radioiodine treatment of nonresectable or incompletely resectable lesions, e.g. microscopic disease, macroscopic local tumour or lymph node or distant metastases, is performed as curative or paliative therapy either as a component of primary treatment of DTC or to address persistent or recurrent disease (Luster et al., 2008). Radioiodine ablation after total or near-total thyroidectomy is a standard procedure in patients with DTC. When radioiodine uptake is scintigraphically proven before or after RAIT, then RAIT of nonresectable or incompletely resectable tumour, e.g. local recurrences, lymph node metastases or disseminated iodineavid lung metastases or other distant lesions, has shown to be effective in eradicating disease, slowing disease progression or providing symptomatic relief (Durante et al., 2006). Decision on whether or not to give RAIT with the intention of cure or palliation should be individualised to the patient and should consider several factors, among others also the patient health status — inability to tolerate surgery or other potential therapeutic interventions, e.g. chemotherapy.

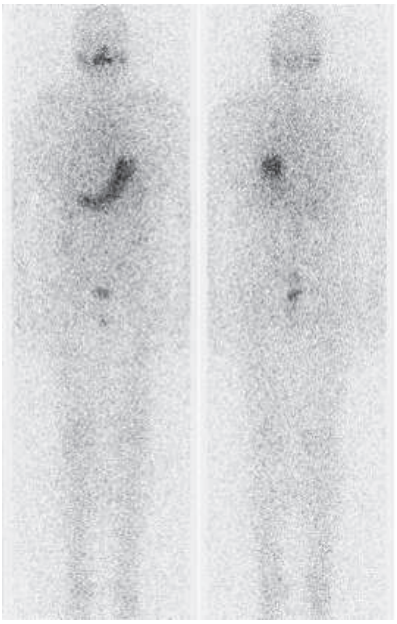

Fig. 6. Diagnostic whole-body scintigraphy - normal finding

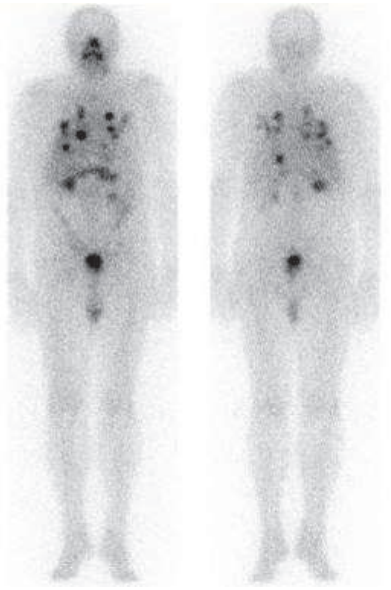

Fig. 7. Post-therapy whole-body scintigraphy. Multiple lung metastases which accumulate radioiodine

It can make RAIT the preferred or the only therapeutic option; conversely, where use of recombinant human thyroid-stimulating hormone (rhTSH) is not economically feasible, inability to tolerate hypothyroidism could rule out RAIT.

Absolute contraindications of RAIT is pregnancy and breastfeeding (as in RAIT in hyperthyroidism).

The effectiveness of RAIT depends on the patient's serum TSH level being sufficiently elevated. A TSH level of ≥30 mU/l is believed to increase sodium iodine symporter (NIS) expression and thereby to optimise radioiodine uptake (Cooper et al., 2006). Such TSH elevation can be reached by waiting at least 3 weeks after thyroidectomy or 4–5 weeks after discontinuing treatment with levothyroxine (T4). Triiodothyronine (T3) may be substituted for T4 until 2 weeks before RAIT in an attempt to decrease the duration of hypothyroidism. When thyroid hormone is withheld, it should be initiated or resumed 2 days after radioiodine administration. Traditional thyroid hormone withdrawal has the major drawback of causing weeks to months of hypothyroid symptoms in most patients (Duntas & Biondi, 2007, Luster et al., 2005, Dow et al., 1997, Schroeder et al., 2006). Such physical and psychological morbidity may include fatigue, depression, impaired ability to concentrate, sleep disturbance, weight gain, constipation, dry skin, hoarseness, puffy face or hands, cardiovascular abnormalities, impaired renal function and exacerbation of dyslipidemia (Billewicz et al., 1969, Botella-Carretero et al., 2003, 2004, 2005, 2006, Luster et al., 2005, Tagay et al., 2005). These manifestations in turn frequently significantly decrease patient quality of life, cause absenteeism from or impaired performance in work or study or lead to debilitating or even life-threatening worsening in psychological, cardiovascular, renal or other concomitant conditions (Borget et al., 2007, Dow et al., 1997, Duntas & Biondi, 2007,

Haugen et al., 1999, Ladenson et al., 1997, Leclere et al., 2000, Luster et al., 2005, Nijhuis et al., 1999, Schroeder et al., 2006).

An alternative to thyroid hormones withdrawal for attaining TSH elevation is rhTSH administration. In Europe and elsewhere, this drug has been approved for use in adults as preparation for serum Tg testing, dxWBS or both or for radioiodine ablation (Luster, 2006).

Radiosensitivity of thyroid gland is relatively high. For destruction and ablation of normal thyroid gland is needed higher activity than for destruction of tumor tissue.

Because of the larger dose of radioiodine and the lower uptake by the tissue in thyroid cancer, more side effects can be seen, particularly transient sialoadenitis, than in the therapy of hyperthyroidism. The mortality of patients treated with less than total thyroidectomy and limited ^{131}I treatment was found to be three to four times higher than that of patients treated with total thyroidectomy and RAIT to ablate known foci of radioiodine uptake. Thyroglobulin is the major tumour marker for thyroid cancer of the follicular epithelium. It is not only specific for tumour tissue but is also specific component of normal thyroid tissue. Since thyroglobulin is produced exclusively by thyroid tissue, only very small amounts can be found in the blood after thyroidectomy and ablative radioiodine therapy. Any post-therapeutic elevation of its levels indicates either remnant of thyroid tissue, requiring further ablative therapy, or the presence of metastases or local recurrence. Following total or near-total thyroidectomy, TSH elevation reaches a maximum in 4-6 weeks. In the follow-up care, patients are maintained on suppressive doses of thyroid hormone. The goals of follow-up after initial therapy are to maintain adequate levothyroxine (T4) therapy and to detect persistent or recurrent thyroid carcinoma. All patients with thyroid cancer must be treated with thyroid hormone after thyroidectomy for correction of surgically induced hypothyroidism and to suppress stimulated growth of persistent or recurrent thyroid cancer by reducing TSH levels. Thus thyroid hormone therapy ensures „replacement" therapy, which corrects hypothyroidism, and „suppressive" therapy, which inhibits TSH secretion. Thyroid cell proliferation and differentiation is mainly TSH dependent. Therefore TSH secretion must be inhibited by thyroid hormone therapy in all patients with differentiated thyroid cancers. Thyroid hormone is a basic principle that is included in the guidelines of thyroid cancer therapy. Before administration of radioiodine, thyroid homone therapy has to be interrupted for diagnosis or treatment. Radioiodine uptake, thyroglobulin synthesis and its secretion by thyroid cancer cells will be stimulated by increased TSH. Neoplastic as wel as normal thyroid cell differentiation depends on TSH. Accordingly, metastases take up radioiodine only if the patient is hypothyroid with high serum TSH levels, while no uptake is seen when the patient is on hormone suppressive therapy with low or undetectable serum TSH concentrations. Serum TSH level should be taken into account when interpreting the serum thyroglobulin value as the presence or absence neoplastic disease. In most patients with persistent or recurrent neoplastic disease, thyroglobulin concentration will increase dramatically during hypothyroidism following withdrawal of thyroid hormone treatment. If there is histologically confirmed thyroid cancer, then 6-8 weeks after thyroidectomy the patient is admitted for radioiodine thyroablation. The patient comes in a fully developed deep clinical hypothyroidism (TSH level usually above 100 mU/l). To achieve sufficient accumulation of radioiodine in the thyroid remnants it is needed to be TSH higher than 30 mU/l. Then we perform ablation of thyroid remnant by radioiodine, which in addition to destruction of the remaining thyroid tissue removed also possible intrathyroidal metastases.

After radioiodine therapy the suppressive therapy is started. 6 to 12 months after ablation the control whole-body scintigraphy is performed in hypothyroidism after 4 weeks withdrawal of thyroid hormones.

In the postoperative monitoring of patients with differentiated thyroid cancer should be solved a serious problem that is disturbing the patient life. This is hypothyroidism, which is a prerequisite for the implementation of thyroablation, whole body radioiodine scintigraphy and any further RAIT. It must be deep enough, which can be in actively working patients after withdrawal of suppressive therapy considerable difficult. Fortunately the rapid tumor growth is rarely stimulated by a brief rise in TSH concentration. The usual scheme is to carry out the treatment or control of patients during hospitalization after discontinuation of levothyroxine replacement for approximately 4-5 weeks. This has lead to profound hypothyroidism. In a small number of patients on long-term suppressive therapy we have observed only a moderate response to TSH after withdrawal of T4. Another option is to combine T4 and triiodothyronine (T3). Short-term administration of T3 alleviates some of the symptoms of prolonged hypothyroidism and must be stopped 2 weeks before radioiodine administration. This procedure also achieves a corresponding increase in TSH levels and hypothyroid patients subjectively perceived better. The third option is administration of recombinant human thyrotropin (rhTSH - Thyrogen) which stimulates thyroid tissue without requiring the discontinuation of thyroid hormone therapy. rhTSH can be used for diagnostic purposes (determination of thyroglobulin, scintigraphy) and before RAIT. Thyrogen should be used in patients who are either unable to mount an adequate endogenous TSH response to thyroid hormone withdrawal or in whom withdrawal is medically contraindicated. The use of Thyrogen allows for radioiodine imaging while the patient are euthyroid on levothyroxine. The clearance of radioiodine is approximately 50% greater in euthyroid patients than in hypothyroid patients, who have decreased renal function. Thus, radioiodine retention is less in euthyroid patients at the time of imaging and this factor should be considered when selecting the activity of radioiodine for imaging. Thyrotropin also stimulates the production of thyroglobulin and increases the usefulness of this tumour marker in patients treated with thyroid hormone who have had thyroid tissue ablated. For its high price Thyrogen unfortunately cannot be used in all patients with thyroid cancer.

Suppression of endogenous secretion of TSH should be always maintained in patients with differentiated thyroid cancer. In low risk patients considered as cured, the levothyroxine dose is modified to maintain a low but detectable serum TSH concentration (0,1 to 0,5 mU/l). In high risk patients with persistent/recurrent disease and even those considered as cured, higher doses of levothyroxine are continued, with the objective of attaining a serum TSH level of 0,1 mU/l or less, the free triiodothyronine concentration should be maintained within the normal range to avoid any significant overdosage. Reduction of serum thyroglobulin concentration is achieved with doses of thyroid hormone that reduce serum TSH to very low levels.

5. Conclusion

This chapter describes treatment options for some kinds of benign thyroid disease and differentiated thyroid cancers with radioactive iodine and context of this therapy with the development of post-radiation hypothyroidism. Moreover, deliberately induced

hypothyroidism by thyroablation and in the further course also by the withdrawal of substitution and suppressive thyroid hormone therapy is used in the diagnosis and treatment of differentiated thyroid carcinomas.

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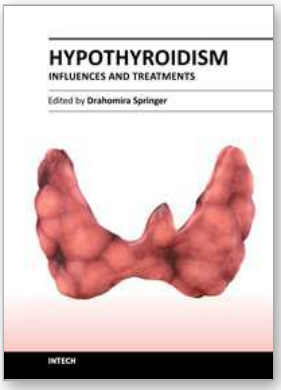

Hypothyroidism - Influences and Treatments

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Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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