Marija Miletić[1], Miloš Stojanović, Biljana Nedeljković Beleslin, Mirjana Stojković, Jasmina Ćirić, Miloš Žarković

TAKING ALL THE SIDEROADS OF HYPERTHYROIDISM THERAPY – PITFALLS AND POSSIBILITIES

Abstract: There are three basic modalities for the treatment of thyrotoxicosis: thyrosuppresive drug therapy, ablation with radioactive iodine and surgical treatment. Patients who do not achieve adequate thyrotoxicosis control, as was the case of described patient, have a high mortality rate due to the possibility of developing a thyroid storm. The use of drug therapy for hyperthyroidism, as the first line of treatment, is associated with the appearance of various side effects, as was the case in our patient. Side effects of Methimazole are dose-dependent, while in the case of Propylthiouracil, the occurrence of side effects is not clearly dose-dependent. In the case of the described patient, all alternative, lesser known modalities for the treatment of hyperthyroidism were applied, after the occurrence of adverse reactions to thyrosuppressive therapy. Sodium perchlorate, ie. Sodium with perchloric acid is rarely used in the treatment of hyperthyroidism, as in cases of severe idiosyncratic reactions to thionamides, agranulocytosis or hepatitis, if the eumetabolic state is not achieved and the application of a therapeutic dose of radioiodine is not possible. It is applied in the form of a solution, usually 8%; In more severe forms of the disease, when hyperthyroidism is very pronounced, 10 to 15 drops a day are given 4 to 6 times and the dose is sometimes reduced to the minimum maintenance dose. After the adverse reaction even to sodium perchlorate therapy we were left with one more, last option- Plasma Therapy exchange. Plasma Therapy Exchange (TPE) is an out-of-body blood purification technique designed to remove high-molecular-weight substances bound to plasma proteins (autoantibody pathogens, immunocomplexes, cryoglobulins, myeloma light chains, endotoxins, lipoprotein-containing cholesterol, and thyroid). The effectiveness of treatment depends on the volume of

[1] Odeljenje za oboljenja štitaste žlezde, Klinika za endokrinologiju, dijabetes i bolesti metabolizma, Klinički centar Srbije, Email adresa: drmariamiletic@gmail.com

blood being processed, the volume of plasma exchanged in each process, the number of procedures performed, the frequency of exchange and the rate of mobilization, stabilization and re-synthesis of cells or plasma components. TPE is an effective alternative treatment that provides an opportunity to prepare patients for definitive treatment: ablative therapy such as RAI ablation or thyroidectomy. Therapeutic plasmapheresis, if performed in specialist centers, is a safe, fast and effective method.

Key words: Hyperthyreosis, drug adverse effects, Potassium iodine, Sodium perchlorate, Plasma Exchange therapy

Case report

Patient AJ, 36 years old, complains of weight loss, malaise, nervousness, insomnia, sweating, trembling hands, absence of menstruation. Hyperthyroidism was diagnosed in June 2019, when Tiastat was introduced into therapy, after which changes in the skin characteristics of urticaria occurred, and the drug was replaced by Propylthiouracil (PTU). Shortly after the introduction of the drug, there was scratching in the throat, skin manifestations of the erythema type, she noticed that her whites were yellowed. Drug induced hepatitis was diagnosed, after which the therapy was stopped, and the liver enzymes soon returned to normal. In her personal anamnesis, she states a pollen allergy, is a smoker. Family anamnesis is without peculiarities. The patient is conscious, well oriented, TT 62 kg, TV171 cm, BMI 21 kg / m2, afebrile, at rest eupnoic, acyanotic, neatly colored, velvety, sweaty skin, neatly hydrated, without peripheral lymphadenopathy, pronounced efflorescences and signs of hemorrhagic syndrome. Neck: cylindrical, actively and passively movable. The veins of the neck are inconspicuous. Thyroid gland is enlarged, soft, painfully insensitive to palpation, mobile when swallowing, without palpable nodules and regional lymph nodes. Percussion present sonority, auscultatory normal respiratory sound, without accompanying findings. Heart rate arrhythmic, fr 120 / min, yew tones, TA 100/60 mmHg. ECG: Sinus tachycardia, fr. 24 in min., Without changes in ST segment or T wave. Radiography of the heart and lungs neat. Neck ultrasound: The thyroid gland is laid lower, enlarged, isthmus about 10 mm thick. The parenchyma of the gland is hypoechogenic, homogeneous, with an enhanced CD signal, pseudonodulated. Paratracheal LN are up to 10 mm in diameter. There are no pathologically altered lymph nodes in the jugular chains. Both submandibular and parotid glands have a homogeneous echostructure, without focal changes (TIRADS DL1 LL1). Abdominal ultrasound of normal findings. Thyroid status on admission: Thyrostimulating hormone (TSH): <0.005 mIU / L [0.27 – 4.2], Thyroxine free (fT4): > 100.0 pmol / L [12.0 – 22.0] Triiodothyronine, free (fT3): 44.85 pmol / L [3.1 – 6.8], Antibodies to thyroid peroxidase (anti-TPO):

66.0 IU / L [0.0 – 34.0], Antibodies to thyroglobulin (anti-TG): 632.0 IU / L [0.0 – 115.0] TSH receptor antibodies: 7.0 IU / L.

KJ (Potassium iodide, Lugol's solution), 3 x 7 gtt with Pronisone tbl 20 + 10 mg, was introduced into the therapy. Thyroid status progressivly: fT4: 77.8… 60.9… .44.5… .41.3 pmol / L, fT3: 19.33… 13.55… .10.45… 10.41 pmol / L. In the further course of the disease on the 18th day after the introduction of therapy, the effects of KJ elude: FT4 44.4, FT3 22.1 pmol / l. At her own request and responsibility, the patient is discharged to undergo therapy with Na-perchlorate (NaClO4) at a dose of 4 x 15 gtt, and then 5 x 21 gtt, after which she develops fever, diarrhea and leukocytopenia, as part of the sdverse drug reaction. NaClO4 therapy was discontinued and treatment with high doses of beta-blockers was continued until hospitalization. Immediately after discontinuation of therapy, the discomfort and fever subsided. Radioactive iodine fixation test (RAI) was performed, percentage of fixation after 24 h: 56.4%. A decision was made to treat with radioactive iodine, with prior application of plasmapheresis. Therapeutic Plasma Exchange (TPE) was performed in five cycles, without adverse events, with an adequate response and a decrease in thyroid hormone concentration (FT3> 50 pmol / l… 5.92 mol / l, FT4> 100 pmol / l … 15.9 pmol / l The patient was referred to the Center for Nuclear Medicine, KCS, where she received radioiodine therapy, after which Pronison tbl 2 x 20 mg was introduced into therapy.The patient was discharged in good general condition, biochemically euthyroid, with therapy: Propranolol tbl 3x60 mg, Pronison tbl 20 + 10 mg, Nolpaza tbl 40 mg, with regular check-ups every 14 days.

The use of drug therapy for hyperthyroidism, as the first line of treatment, is associated with the appearance of various side effects. Side effects of Methimazole are dose-dependent, while in the case of Propylthiouracil, the occurrence of side effects is not clearly dose-dependent. Side effects can be divided into "minor" and "major" forms. "Minor" or mild side effects occur with equal representation in both drugs. They include skin changes (usually urticaria or macular rash) that occur in 4-6%, gastrointestinal problems (1-5%), arthralgia (1-5%) and mild transient granulocytopenia with equal representation for both types of drug. Changes in taste and smell, sialodenitis and headaches can also occur very rarely. Mild skin reactions can be resolved by adding antihistamines while thyrosuppressive therapy is continued. Alternatively, the patient may be switched from one antithyroid drug to another. However, a cross-reaction can exist in about 50%. The onset of arthralgia, although a "minor" side effect, requires immediate discontinuation of the drug, as it can lead to very severe migratory polyarthritis known as "antithyroid arthritis syndrome". Major or severe side effects occur in 0.2-0.5% of treated patients and include polyarthritis, ANCA-positive vasculitis, hepatotoxicity (immunoallergic hepatitis and cholestasis), agranulocytosis, and very rarely thrombocytopenia, aplastic anemia, hypoglycaemia.

During 1993 a possible association of antimyeloperoxidases of antineutrophil cytoplasmic antibodies (MPO-ANCA) with the use of antithyroid drugs has been

reported with the possibility that antibodies to microsomal antigens consisting mainly of thyroid peroxidase may cross-react with MPO. Hepatotoxicity is another severe complication of thyrosupressive therapy, which occurs in 0.1-0.2% of cases. There are two types of drug hepatotoxicity and these are direct toxicity and idiosyncrasy. Thyrosupressive drugs lead to liver lesions by type of idiosyncrasy. The onset of the lesion is unpredictable, the response is not dose dependent and can occur at any time during therapy. Extrahepatic hypersensitivity reactions, such as rash, fever, arthralgia, leukocytosis and eosinophilia, exist in a quarter of patients, which together with the course of the disease suggests that these are immune-mediated reactions. Recent results show that in most cases and in idiosyncratic reactions, there is direct hepatotoxicity, but caused by metabolites more often than by intact drugs. The drug or its metabolite binds to the cellular component of the host, creating a hapten, and the immune response to this neoantigen plays a role in the pathogenesis of the liver lesion. Methimazole and Carbimazole cause cholestasis, while Propylthiouracil causes hepatocyte necrosis. Due to the different mechanisms of hepatotoxicity, the use of an alternative antithyroid drug is possible in further treatment. Agranulocytosis is the most serious complication of thyrosupressive therapy.

The use of stable iodide in the treatment of hyperthyroidism has been known since the era of Von Basedov (1840) and Trousseau (1863) (1-5). Although iodide was used during the 19th and early 20th centuries, this form of therapy was widely accepted following the insightful observations of Neiser (1920), Loevi and Zondek (1921), and Plummer (1923) (1, 4). Namely, Plummer introduced 10 drops of Lugol's solution containing 5% I2 and 10% potassium iodide (KI) into the therapy, in a dose of approximately 80–320 mg of iodine per day (5). Beginning in the 1930s, Thompson et al (2) reported satisfactory results after giving patients approximately 6 mg of iodine daily in 64% of mild and 10% of severe cases of Graves-Based hyperthyroidism.

However, the medical literature contains plenty of references on the risks of administering iodine substrates to patients with hyperthyroidism. Iodide therapy brought temporary relief, but evasion of its effects worsened the patient's clinical condition (1). Stanburry reported iodine-induced hyperthyroidism in 1998, but as a complication that arose when iodine was given for endemic goiter (6), in addition to a few reports in the non-endemic area (7). Following the introduction of thionamide and radioactive iodine (RI) therapy, iodide has not been used in the medical treatment of hyperthyroidism (1). Following the introduction of assays to determine thyroid hormones and TSH levels, the initial effects of excess iodide (150–456 mg) on lowering serum T4 levels were confirmed in most studies (8–12). Although persistently elevated T3 levels and the onset of an "escape" mechanism have been reported after 2–14 weeks (8, 9), some patients have reached euthyroid status and maintained normal T4 and T3 levels for several months (8, 9). Interestingly, the mechanisms of inhibitory action of excess iodide on the thyroid gland were elucidated after the use

of iodide became less common for the medical treatment of hyperthyroidism, except for preoperative preparation or in a thyrotoxic crisis. In 1948, Wolff and Chaikoff (21) reported that organic I- binding in the white rat thyroid was blocked when plasma I2 concentrations reached a critically high threshold (200–350 mg / L or 1.6–2.8 mM). By using fresh rat thyroid lobes giving excellent amounts of iodothyronine in vitro, inhibitory effects on T3 or T4 synthesis became apparent when iodide concentrations were greater than 2.5 mM (22). This phenomenon, known as the acute Wolff-Chaikoff effect, which suggests the principle of "Too bad as well as too little", is explained by the formation of organic iodine compounds, such as iodohexadecanal, which can be involved in autoregulatory processes in the thyroid gland (23). However, inhibitory effects have been shown to be transient due to a decrease in I-transport induced by decreased Na + / I-importer activity (24).

Inhibition of iodide organization may partially explain the clinical effect of excess iodide on Graves' hyperthyroidism (25, 26). However, the effect of iodide on the reduction of serum thyroxine levels in Graves' hyperthyroidism occurs earlier than with thionamide therapy (1, 27). It has been suggested that, unlike thionamide, excess iodide affects almost all important aspects of iodine metabolism in the thyroid gland, including not only iodine organization but also cAMP production, vascularity, iodide transport, conjugation, and thyroxine secretion (27, 28). Moreover, necrosis of human thyroid epithelial cells was induced in the presence of more than 10 mM KI (29). It is not clear why evasion of excess iodide is common in untreated patients with Graves 'hyperthyroidism despite increased iodide intake (25, 26), while iodide-induced hypothyroidism is common in chronic thyroiditis (30-32) and irradiated or operated patients with Graves' hyperthyroidism. 13).

The results of a study by Okamura et al showed that some patients with Graves' hyperthyroidism were also sensitive to supraphysiological iodide concentrations, and iodide therapy alone was effective in 66% of patients who showed side effects with thionamide drugs after increasing the dose of KI to more than 100 mg. daily. Interestingly, a decrease in TBII activity and a decrease in goiter resulting in remission were observed in 38.6% after 5–23 years of iodide therapy. It is controversial whether thionamide drugs have immunosuppressive effects (33). The results of the Okamura study, together with the findings of a report on the reduction of TBII after perchlorate therapy (34), are not consistent with the concept of direct immunosuppressive effects of thionamide drugs. Although iodine-deficient animals have been shown to be highly sensitive to the Wolff-Chaikoff effect (35), the mechanisms underlying differences in sensitivity to excess iodide in iodine-deficient areas the suffixes are unknown (25). Considering the estimated iodine content of the thyroid gland and total body iodine of 10 and 15 mg, respectively (36), a large amount of iodide is required to maintain a sufficient content of intrathyroid iodine to suppress thyroid function, possibly by passive I-transport.

Further studies are needed to determine ways to predict patient responses to KI therapy. However, remission was observed in 70.8% of patients whose condition was controlled with less than 200 mg of CI, compared with only 35.0% of patients who required 200 mg or more of CI, suggesting that the chance of remission was low in patients insensitive to CI.

The advantage of KI therapy is that its effects are reversible, without serious side effects, such as leukocytopenia or liver damage. Induction of hypothyroidism (13, 18, 30–32) or transient increase in TBII activity (20) may reflect iodide-induced morphological (29), chemical (32) or immunological (31) perturbations in the thyroid gland. Because dose reduction of KI may cause worsening of thyrotoxicosis in Graves' hyperthyroidism, patients were treated with combination therapy containing KI and synthetic L-thyroxine. To date, no evidence has been found that excess iodide affected organs without Na + / I− symporters, but further studies are needed to assess the safety of chronic KI therapy. There is speculation that a reduced amount of iodide ions in thyroid cells is a direct stimulus of cellular activity (38). Thyrocytes in diffuse toxic goiter may behave as if they are iodine deficient, when in fact they are not iodine-deficient. Ingbar (38) proposed the hypothesis of thyroid self-regulation, which suggests that the manifestations of Graves' disease may affect, at least in part, the gland that has lost the ability to sense its own iodine content and hence activates autoregulatory mechanisms that modulate thyroid function and growth. – so-called thyroid reset, iodostat. A study by Okamura et al suggests that pharmacological doses of iodide may redirect many functional, anatomical (probably by involution) (39), and immune abnormalities of diffuse toxic goiter after a long clinical course when thyroid hyperplasia is mild or reversible. Following the analysis of the Japanese study, it must be emphasized that if patients preferred KI therapy after showing side effects with thionamide, continuous administration of a large amount of KI was required until remission, and that a rapid reassessment of treatment was required when evasion occurred. or when treatment for more than 3 months required more than 200 mg of KI per day. Perchlorate is an inorganic anion that is a potent competitive inhibitor of sodium iodide-importer (NIS) on the basolateral membrane of thyroid cells. At pharmacological doses, perchlorate reduces the active transport of iodine in the thyroid gland. During the 1950s, perchlorate (in large doses of 600-1000 mg per day) was used to treat hyperthyroidism. Its use has decreased after several cases of aplastic anemia were noticed. In the early 1980s, perchlorate at doses up to 900 mg per day was used in therapeutic protocols to treat Graves' disease without serious side effects (41). In recent decades, lower doses have been used safely and effectively in the treatment of Graves' disease and iodine-induced hyperthyroidism (42). NIS has also been identified at the molecular level of some extrathyroid tissues, such as the lactating mammary gland (where iodine concentration would be beneficial for the newborn), salivary glands and gastric and intestinal mucosa, in which the physiological functions of iodide transport are still incompletely elucidated (43).

Plasma Therapeutic Exchange (TPE) is an out-of-body blood purification technique designed to remove high molecular weight substances bound to plasma proteins (autoantibody pathogens, immunocomplexes, cryoglobulins, myeloma light chains, endotoxins, cholesterol-containing lipoproteins and thyroid hormones). Indications for apheresis only for thyrotoxicosis have been established by the American Society for Apheresis within category III (44). Category III recommends that previous assessments have been inadequate and that the decision on this therapeutic modality is individual. The effectiveness of treatment depends on the volume of blood being processed, the volume of plasma exchanged in each process, the number of procedures performed, the frequency of exchange and the rate of mobilization, stabilization and re-synthesis of cells or plasma components (45,46). Like any invasive procedure, TPE also has complications.

Bleeding, hematomas and / or infections are associated with catheter use, as well as coagulation disorders, hypocalcaemia, hypotension, transfusion reactions, transfusion-transmitted diseases, pulmonary edema and / or pulmonary embolism. Albumin or fresh frozen plasma (FFP) is used as a fluid replacement in TPE in the treatment of thyrotoxic patients (45, 46). Through the prism of the literature and based on the experience of the KCS Department of Thyroid Diseases, TPE is an effective alternative treatment that provides the opportunity to prepare patients for definitive treatment: ablative therapy such as RAI ablation or thyroidectomy. Therapeutic plasmapheresis, if performed in specialist centers, is a safe, fast and effective method.

Conclusion:

There are three basic modalities for the treatment of thyrotoxicosis: drug therapy with thyrosuppressants, ablation with radioactive iodine and surgical treatment. Patients who do not achieve adequate control of thyrotoxicosis have a high mortality due to the possibility of developing a thyroid storm. The use of drug therapy for hyperthyroidism, as the first line of treatment, is associated with the appearance of various side effects, as was the case of presented patient. Side effects of Methimazole are dose-dependent, while in the case of Propylthiouracil, the occurrence of side effects is not clearly dose-dependent. In the case of the described patient, all alternative, lesser known modalities for the treatment of hyperthyroidism were applied, after the appearance of adverse reactions to thyrosuppressive therapy. Sodium perchlorate, ie. Sodium with perchloric acid is rarely used in the treatment of hyperthyroidism, as in cases of severe idiosyncratic reactions to thionamides, agranulocytosis, hepatitis, if the eumetabolic state is not achieved and the application of a therapeutic dose of radioiodine is not possible. It is applied in the form of a solution, usually 8%; In more severe forms of the disease, when hyperthyroidism is very pronounced, 10 to 15 drops a day are given 4 to 6 times and the dose is sometimes reduced to the minimum

maintenance dose. Plasma Therapy (TPE) is an out-of-body blood purification technique designed to remove high molecular weight substances bound to plasma proteins (autoantibody pathogens, immunocomplexes, cryoglobulins, myelomotor-containing endopoxy light chains) and thyroid hormones). The effectiveness of treatment depends on the volume of blood being processed, the volume of plasma exchanged in each process, the number of procedures performed, the frequency of exchange and the rate of mobilization, stabilization and re-synthesis of cells or plasma components. TPE is an effective alternative treatment that enables the preparation of patients for definitive treatment in which other therapeutic modalities, such as the presented patient, cannot establish adequate metabolic control: ablative therapy such as RAI ablation or thyroidectomy. Therapeutic plasmapheresis, if performed in specialist centers, is a safe, fast and effective method.

References

1. Astwood EB. Thyroid and antithyroid drugs. In: Goodman LS, Gilman A, eds. The Pharmacological Basis of Therapeutics. 3rd ed. New York: The Macmillan Company; 1965: 1466–1503.
2. Thompson WO, Thompson PK, Brailey AG, Cohen AC. Prolonged treatment of exophthalmic goiter by iodine alone. Arch Intern Med. 1930; 45: 481–502.
3. Volpe R, Johnston MW. The effect of small doses of stable iodine in patients with hyperthyroidism. Ann Intern Med. 1962; 56: 577–589.
4. Plummer HS. Results of administering iodine to patients having exophthalmic goiter. JAMA. 1923; 80: 1955.
5. Plummer HS, Boothby WM. The value of iodin in exophthalmic goiter. J Iowa Med Soc. 1924;14: 66–73.
6. Stanbury JB, Ermans AE, Bourdoux P, et al. Iodine-induced hyperthyroidism: occurrence and epidemiology. Thyroid. 1998; 8: 83–100.
7. Vagenakis AG, Wang CA, Burger A, Maloof F, Braverman LE, SH. Iodide-induced thyrotoxicosis in Boston. N Engl J Med. 1972; 287: 523–527.
8. Emerson CH, Anderson AJ, Howard WJ, Utiger RD. Serum thyroxine and triiodothyronine concentrations during iodide treatment of hyperthyroidism. J Clin Endocrinol Metab. 1975; 40: 33–36.
9. Philippou G, Koutras DA, Piperingos G, Souvatzoglou A, Moulodoi: The effect of iodide on serum thyroid hormone levels in normal persons, in hyperthyroid patients, and in hypothyroid patients on thyroxine replacement. Clin Endocrinol (Oxf). 1992; 36: 573–578.
10. Roti E, Robuschi G, Manfredi A, et al. Comparative effects of sodium ipodate and iodide on serum thyroid hormone concentrations in patients with Graves' disease. Clin Endocrinol (Oxf). 1985; 22: 489–496.
11. Tan TT, Morat P, Ng ML, Khalid BA. Effects of Lugol's solution on thyroid function in normals and patients with untreated thyrotoxicosis. Clin Endocrinol (Oxf). 1989; 30: 645–649.

12. Feek CM, Sawers JS, Irvine WJ, Beckett GJ, Ratcliffe WA, Toft AD. Combination of potassium iodide and propranolol in preparation of patients with Graves' disease for thyroid surgery. N Engl J Med. 1980; 302: 883– 885.
13. Braverman LE, Woeber KA, Ingbar SH. Induction of myxedema by iodide in patients euthyroid after radioiodine or surgical treatment of diffuse toxic goiter. N Engl J Med. 1969; 281: 816–821.
14. Okamura K, Ikenoue H, Shiroozu A, Sato K, Yoshinari M, Fujishima M. Reevaluation of the effects of methylmercaptoimidazole and propylthiouracil in patients with Graves' hyperthyroidism. J Clin Endocrinol Metab. 1987; 65: 719–723.
15. Cooper DS. Antithyroid drugs. N Engl J Med. 2005; 352: 905–917.
16. Ikenoue H, Okamura K, Sato K, et al. Prediction of relapse in drugtreated Graves' disease using thyroid stimulation indices. Acta Endocrinol (Copenh). 1991;125: 643–650.
17. Okamura K, Sato K, Ikenoue H, et al. Reevaluation of the thyroidal radioactive iodine uptake test, with special reference to reversible primary hypothyroidism with elevated thyroid radioiodine uptake. J Clin Endocrinol Metab. 1988; 67:720–726.
18. Sato K, Okamura K, Yoshinari M, et al. Reversible primary hypothyroidism and elevated serum iodine level in patients with renal dysfunction. Acta Endocrinol (Copenh). 1992; 126: 253–259.
19. Yoshinaga J, Morita M. Determination of iodine in biological fluids by ICP-MS. Biomed Res Trace Elements. 1991; 2: 143–144.
20. Wilson R, McKillop JH, Thomson JA. The effect of pre-operative potassium iodide therapy on antibody production. Acta Endocrinol (Copenh). 1990; 123: 531–534.
21. Wolff J, Chaikoff IL. Plasma inorganic iodide as a homeostatic regulator of thyroid function. J Biol Chem. 1948; 174: 555–564.
22. Okamura K, Sato K, Fujishima M. Reversible or irreversible thyroid dysfunction in Hashimoto thyroiditis. In: Nagataki S, Mori T, Torizuka K, eds. 80 Years of Hashimoto Disease. Amsterdam, The Netherlands: Elsevier Science Publishers; 1993: 149–154.
23. Pisarev MA, Gärtner R. Autoregulatory action of iodine. In: Braverman LE, Utiger RD, eds. Werner, Ingbar's The Thyroid. A Fundamental and Clinical Text. 8th ed. Philadelphia, PA: Lippincott Williams, Wilkins; 2000: 85–90.
24. Eng PH, Cardona GR, Fang SL, et al. Escape from the acute WolffChaikoff effect is associated with a decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein. Endocrinology. 1999; 140: 3404–3410.
25. Harden RM, Koutras DA, Alexander WD, Wayne EJ. Quantitative studies of iodine metabolism in iodide-treated thyrotoxicosis. Clin Sci. 1964; 27: 399–405.
26. Stewart RD, Murray IP. Effect of small doses of carrier iodide upon the organic binding of radioactive iodine by the human thyroid gland. J Clin Endocrinol Metab. 1967; 27: 500–508.
27. Nagataki S. Effect of excess quantities of iodide. In: Greep RO, Astwood EB, eds. Handbook of Physiology. Volume III. Thyroid. Washington, DC: American Physiological Society; 1974: 329–344.
28. Taurog AM. Thyroid hormone synthesis: thyroid iodine metabolism. In: Braverman LE, Utiger RD, eds. Werner, Ingbar's the Thyroid. A Fundamental and Clinical Text. 8th ed. Philadelphia, PA: Lippincott Williams, Wilkins; 2000: 61–85.

29. Many MC, Mestdagh C, van den Hove MF, Denef JF. In vitro study of acute toxic effects of high iodide doses in human thyroid follicles. Endocrinology. 1992; 131: 621–630.
30. Braverman LE, Ingbar SH, Vagenakis AG, Adams L, Maloof F. Enhanced susceptibility to iodide myxedema in patients with Hashimoto's disease. J Clin Endocrinol Metab. 1971; 32: 515–521.
31. Okamura K, Inoue K, Omae T. A case of Hashimoto's thyroiditis with thyroid immunological abnormality manifested after habitual ingestion of seaweed. Acta Endocrinol (Copenh). 1978; 88: 703–712.
32. Sato K, Okamura K, Hirata T, et al. Immunological and chemical types of reversible hypothyroidism; clinical characteristics and longterm prognosis. Clin Endocrinol (Oxf). 1996; 45: 519–528.
33. Weetman AP, McGregor AM, Hall R. Evidence for an effect of antithyroid drugs on the natural history of Graves' disease. Clin Endocrinol (Oxf). 1984; 21: 163–172.
34. Wenzel KW, Lente JR. Similar effects of thionamide drugs and perchlorate on thyroid-stimulating immunoglobulins in Graves' disease: evidence against an immunosuppressive action of thionamide drugs. J Clin Endocrinol Metab. 1984; 58: 62–69.
35. Inoue K, Taurog A. Acute and chronic effects of iodide on thyroid radioiodine metabolism in iodine-deficient rats. Endocrinology 1968; 83:279 –290.
36. Hays MT. Estimation of total body iodine content in normal young men. Thyroid. 2001; 11: 671–675.
37. Lippe BM, Landaw EM, Kaplan SA. Hyperthyroidism in children treated with long term medical therapy: twenty-five percent remission every two years. J Clin Endocrinol Metab. 1987; 64: 1241–1245.
38. Ingbar SH. Autoregulation of the thyroid. Response to iodide excess and depletion. Mayo Clin Proc. 1972; 47: 814–823.
39. Rienhoff WF Jr. Involutional or regressive changes in the thyroid gland in cases of exophthalmic goiter and their relation to the origin of certain of the so-called adenomas. Arch Surg. 1926; 13: 391–425.
40. Bazailai D, Sheinfeld M. Fatal complication following use of potassium perchlorate in thyrotoxicosis. Israel Journal of Medical Sciences. 1966; 2: 453–456.
41. Wenzel KW, Lente JR. Similar effects of thionamide drugs and perchlorate on thyroid-stimulating immunoglobulins in Graves' disease: evidence against an immunosuppressive action of thionamide drugs. The Journal of Clinical Endocrinology and Metabolism. 1984; 58: 62–69.
42. Martino E, Aghini-Lombardi F, Mariotti S, et al. Treatment of amiodarone associated thyrotoxicosis by simultaneous administration of potassium perchlorate and methimazole. Journal of Endocrinological Investigation. 1986; 9: 201–207.
43. De La Vieja A, Dohán O, Carrasco N. Molecular analysis of the sodium/iodide symporter: impact on thyroid and extrathyroid pathophysiology. Physiological Reviews. 2000; 80: 1083–1085.
44. J. Schwartz, A. Padmanabhan, N. Aqui, R.A. Balogun, L. Connelly-Smith, M. Delaney, N.M. Dunbar, V. Witt, Y. Wu, B.H. Shaz, Guidelines on the Use of Therapeutic Aphe-

resis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J. Clin. Apher. 31(3), 149–162 (2016).

45. B. C. McLeod, Plasma and plasma derivatives in therapeutic plasmapheresis. Transfusion 52(Suppl 1), 38S–44S (2012).
46. B. C. McLeod, Therapeutic apheresis: use of human serum albumin, fresh frozen plasma and cryosupernatant plasma in therapeutic plasma exchange. Best. Pract. Res. Clin. Haematol. 19(1), 157–167 (2006).