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Editor's page

# The various faces of hyperthyroidism

This edition of JCTE presents highlights in managing patients with hyperthyroidism. It starts out with an important article by Hoermann and colleagues underscoring the biochemically heterogeneous expression of thyroid hormone activities in subclinical/overt hyperthyroidism and exogenous thyrotoxicosis [1]. The authors call for a stronger emphasis on etiological and clinical features rather than focusing entirely and solely on measuring thyroid stimulating hormone (TSH). In their study of 461 patients composed of untreated thyroid autonomy, Graves' disease, and levothyroxine TSH suppressive therapy after thyroidectomy for thyroid carcinoma, they demonstrate that deiodinase activity is markedly reduced in patients with exogenous thyrotoxicosis compared to patients with endogenous hyperthyroidism because of a lack of TSH stimulation, inhibition by levothyroxine, and the absence of a functioning thyroid gland. This deficiency of athyreotic patients leads to a disconnection between TSH, free thyroxine (FT4), and free triiodothyronine (FT3) with homeostatic equilibria expressed differently in exogenous thyrotoxicosis compared to endogenous hyperthyroidism, and the FT3 response to increasing FT4 concentrations being shifted and less responsive in patients treated with levothyroxine. Such LT4-treated patients showed no acceleration of their T3 generation when FT4 reached the upper normal or hyperthyroid reference range. FT4 concentrations into the upper reference range lead to an increased risk of atrial fibrillation, as shown in the Rotterdam study [2]. It is conceivable that achieving the "individual normal" concentration of circulating FT3 on levothyroxine therapy determines whether patients complain of hypothyroid or hyperthyroid symptoms. This phenomenon of different T3 effects may also explain why long-term risk of TSH suppressive therapy on bone deterioration is less/lower compared to the risk of untreated hyperthyroidism, as seen in postmenopausal women treated for thyroid carcinoma [3].

The next article of this special issue of JCTE concerns the diagnosis of hyperthyroidism and underscores that greater vascularization on color Doppler ultrasonography was associated with marked hypoechogenicity, and greater FT4 and TSH-receptor antibody levels [4]. Vita and colleagues mention that any degree of vascularization is possible in the early phases of patients with Hashimoto's thyroiditis. They also mention that the effectiveness of the so-called vascularization index obtainable by superb microvascular imaging has recently been investigated in 80 patients with Hashimoto's thyroiditis and 107 healthy, asymptomatic control individuals in an attempt to identify a cutoff value [5].

The third article in this edition of JCTE discusses the important topic of mental disease in connection with Graves' disease [6]. Bipolar disorder with mania or manic-depressive psychosis can be related to hyperthyroidism but also a decline in T3 can cause depressive and anxiety disorders. This bidirectional relationship is extensively reviewed by Fukao and colleagues [6]. Stress can trigger the onset and recurrences of hyperthyroidism in patients with Graves' disease [7,8]. It is important to be aware that antithyroid medications used to achieve euthyroidism in hyperthyroid patients can alter the mental well-being [9]. On the other hand, primary hypothyroidism has also been observed in patients with mania [10].

In the fourth article of this special JCTE issue, Moleti and colleagues review the diagnosis and management of hyperthyroidism in pregnancy [11]. Gestational transient thyrotoxicosis occurs in approx. 1–5% of pregnancies and usually resolves by the end of the first trimester. In hyperthyroid pregnant women, serum human chorionic gonadotropin (HCG) usually is measured between 100,000 and 500,000 IU/L, such concentrations being capable of stimulating the TSH-receptor. Moleti and colleagues furthermore discuss that Graves' disease and other autoimmune disorders (i.e. multiple sclerosis) usually improve during the second and third trimester of gestation with relapse in the postpartum period [12,13]. A retrospective review of 379 pregnancies in Italy showed that in women treated with methimazole or propylthiouracil, the rates of spontaneous miscarriage and major congenital malformations were not higher than in the general population [14].

Cipolla and colleagues share their experience performing total thyroidectomy on 594 patients with Graves' disease between age 32 y and 56 y underscoring that it is a safe and effective treatment in experienced hands [15]. Most of these patients were women and the majority of patients were euthyroid or mildly hyperthyroid at the time of thyroidectomy. Lugol's iodine solution, commonly used to reduce the risk of intraoperative blood loss, was not routinely administered, and if so, at a dose of 10 drops 3 times daily for 10–12 days before thyroidectomy. Temporary and permanent recurrent laryngeal nerve palsy were recorded in 31 patients (5.2%) and 1 patient (0.16%), respectively. Temporary and permanent hypocalcemia/hypoparathyroidism developed in 241 patients (40.6%) and 3 patients (0.5%), respectively. Of note, incidental parathyroidectomy during thyroid surgery in 141 procedures (69 total thyroidectomies and 72 total thyroid lobectomies) caused transient symptomatic hypocalcemia in 9 patients (6%) and permanent hypocalcemia in 1 patient who underwent a total thyroidectomy and concomitant neck dissection [16]. Near-total thyroidectomy for treating Graves' disease does not seem to be superior to total thyroidectomy with respect to transient postoperative hypoparathyroidism/hypocalcemia [17], and has higher risk of recurrent hyperthyroidism [18].

Zhou and colleagues underscore the important role of neural monitoring during thyroid surgery for Graves' disease in their retrospective series including 55 thyroidectomies and 82 procedures with intermittent intraoperative neuromonitoring (IONM) and 72 procedures with continuous IONM [19]. Fundakowski and colleagues [20] reported that subjective post thyroidectomy voice complaints occur in 30–87% of patients with risk factors for recurrent laryngeal nerve injury

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including revision procedures and surgeon volume [20]. If the surgeon performed 21–25 cases per year, the odds of a complication were 3% vs. 22% for 11–15 cases per year. In their American Head and Neck consensus statement, Fundakowski and colleagues report that a total thyroidectomy in the absence of metastatic disease will commonly achieve a non stimulated thyroglobulin level of 1–2 ng/ml. Sometimes, a remnant of the Ligament of Berry is intentionally left behind in an effort to protect the recurrent laryngeal nerve [20]. Sometimes, patients with Graves' disease are also found to have well differentiated thyroid cancer [21]. Fundakowski and colleagues mention that, in their opinion, in patients with thyroid cancer a non stimulated thyroglobulin level of < 5 ng/ml after a complete extracapsular total thyroidectomy, or < 30 ng/ml after thyroid lobectomy is acceptable [20]. As pointed out by the International Neural Monitoring Study Group in their 2018 guideline, when bilateral vocal cord paralysis occurs after thyroidectomy, it is found to be permanent in 45% of patients [22]. In thyroid cancer patients, optimal timing of completion surgery is less than 3 days or greater than 3 months in an attempt to minimize the risk of postoperative completion thyroidectomy regarding laryngeal nerve recovery [22,23]. Importantly, postoperative vocal cord dysfunction can occur despite normal intraoperative neuromonitoring [24].

Ferrari and colleagues review the role of chemotactic cytokines (chemokines) in patients with hyperthyroidism [25]. The balance between the Th1 and Th2-dependent cytokine and chemokine system is skewed toward Th1 and an excess of interleukin-12 versus interleukin-10 balance in Th1-cytokine mediated disorders such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, type 1 diabetes mellitus, and Graves' disease [12,26,27]. Interestingly, in the current COVID-19 crisis, the disease caused by SARS-CoV-2 is characterized by an overactive immune response with hyperactivation of Th1/Th17-cells leading to release of proinflammatory cytokines and cytokine storm [28].

The concluding article of this special JCTE issue deals with the infiltration of the thyroid gland by non-thyroidal malignancy as an unusual cause of hyperthyroidism [29]. Many tumors can metastasize to the thyroid gland and other endocrine glands [30,31]. In autopsy series, the most common primary cancers are lung cancer, breast cancer, and melanoma. In clinical or surgical series, the most frequent cancer metastasizing to the thyroid gland is renal cancer followed by colorectal cancer, lung cancer, breast cancer, sarcoma, and melanoma [30]. Interestingly, the most common primary tumors metastasizing to the adrenal glands are melanomas, breast, and lung carcinomas and can result in adrenal insufficiency if both adrenal glands are involved [30]. The most common malignancies infiltrating the thyroid identified by Prof. Jonklaas' literature search were breast and lung cancer. Patients presented with clinical features of thyroiditis and often progressed from hyperthyroidism to hypothyroidism. Excluded from this study were patients with primary thyroid malignancy, pre-existing thyroid disease or positive antithyroidal antibodies, patients with HCG-induced hyperthyroidism, with a history of taking tyrosine kinase inhibitor or immunoregulatory therapy, and those becoming hyperthyroid after receiving radiation therapy or receiving any drugs known to cause hyperthyroidism [29]. Hematological malignancies such as lymphoma or chronic lymphocytic leukemia can also result in hyperthyroidism [32]. Interestingly, in patients receiving immune check point inhibitors, a recent study found low frequency of positive antithyroid antibodies in those developing thyroid dysfunction [33]. Patients with non small-cell lung carcinoma, renal cell carcinoma, and metastatic melanoma treated with nivolumab or pembrolizumab who had baseline antithyroidal antibodies checked before anti-programmed cell death protein-1 (PD1) infusion therapy, and whose antithyroidal antibody concentrations increased and who acquired overt thyroid dysfunction during treatment had higher overall survival [34]. Thyroid dysfunction induced by checkpoint inhibitors has recently been reviewed along with other articles in the thyroid field including environmental aspects and cancer [35–39].

When reading again the papers of this JCTE issue as average readers, we felt that most colleagues would find them useful in their daily clinical practice. Enjoy the reading!

## Conflict of interest statement

The authors declare no conflict of interest related to this article.

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