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Best Achievements in Clinical Thyroidology in 2020

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This review highlights the most interesting research in thyroidology conducted in 2020. The publications of interest discussed below dealt with the following topics: thyroid dysfunction, risk of thyroid cancer, molecular diagnostics and new therapeutics for thyroid cancer, and thyroid disease in the coronavirus disease 2019 pandemic era.

Keywords: Thyroid diseases; Thyroid neoplasms; Thyroid hormone; Therapeutics; COVID-19; Molecular diagnostic techniques

INTRODUCTION

In 2020, clinical studies in thyroidology reported outstanding results. Specifically, intriguing questions about thyroid dysfunction and thyroid cancer were answered through well-designed, randomized clinical trials. This review summarizes the important research published in 2020.

METHODS

Original, peer-reviewed research articles published between January 2020 and December 2020 were extracted through an independent literature review. A brief summary of these articles is presented along with their clinical utility or implications. The publications of interest discussed below dealt with the following topics: thyroid dysfunction, risk of thyroid cancer, molecular diagnostics and new therapeutics for thyroid cancer, and thyroid disease in the coronavirus disease 2019 (COVID-19) pandemic era.

HEALTH IMPACTS OF SUBCLINICAL HYPOTHYROIDISM AND THE BENEFITS OF THYROID HORMONE SUPPLEMENTATION

The impacts of subclinical hypothyroidism on cardiovascular morbidity and mortality and the benefits of levothyroxine (LT4) replacement remain inconclusive because only limited prospective cohort studies or randomized controlled trials have investigated LT4 replacement. In February 2020, Inoue et al. [1] sought to clarify to what extent subclinical hypothyroidism is associated with cardiovascular mortality in a representative sample of 9,020 adults in the United States enrolled in the National Health and Nutrition Examination Survey, and demonstrated that cardiovascular disease mediated 14.3% and 5.9% of the associations of subclinical hypothyroidism and high-normal thyroid-stimulating hormone (TSH) levels with all-cause mortality, respectively. This finding suggests that investigations are needed to examine the clinical benefits of medical interventions for people with elevated TSH levels. Following those results,

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two preliminary but important results were reported from double-blind, randomized controlled trials of LT4 replacement in subjects with subclinical hypothyroidism. Jabbar et al. [2] investigated the effects of LT4 in patients with subclinical hypothyroidism presenting with acute myocardial infarction, but failed to show any benefits for outcomes such as left ventricular function, adverse events, and quality of life after 52 weeks of LT4 treatment. Furthermore, de Montmollin et al. [3] reported that LT4 replacement failed to improve hypothyroid symptoms or tiredness scores at 1 year in subjects aged ≥65 years with subclinical hypothyroidism (4.6≤ TSH ≤11.9 mU/L) in a secondary analysis of the randomized, placebo-controlled Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism Trial (TRUST).

During pregnancy, maternal deficiency of thyroid hormone is associated with low birth weight [4]; however, the impact of subclinical hypothyroidism has remained unclear. A recent systematic review and individual-participant data meta-analysis of 48,145 mother-child pairs from 36 cohorts [5] provided evidence that maternal subclinical hypothyroidism during pregnancy (n=1,275) was associated with a higher risk of small for gestational age (SGA; odds ratio [OR], 1.24; 95% confidence interval [CI], 1.04 to 1.48) and lower birthweight, while isolated hypothyroxinemia (n=929) was associated with a lower risk of SGA (OR, 0.7; 95% CI, 0.55 to 0.91) and higher birthweight. There was an inverse, dose-response association of maternal TSH and free thyroxine (T4; even within the normal range) with birthweight, suggesting the rationale of thyroid function screening during the prenatal period for better postpartum outcomes.

NEW THERAPEUTIC AGENTS FOR GRAVES' DISEASE

Graves' disease is characterized by the presence of auto-antibodies that stimulate the TSH receptor, resulting in hyperthyroidism. The first-line treatment of thyrotoxicosis is thionamide, an anti-thyroid drug (ATD) [6]. A randomized trial investigated the efficacy of a blocking dose of ATD with LT4 replacement compared to ATD monotherapy dose titration. The primary outcome was the percentage of patients with normal TSH levels between 6 months and 3 years after treatment, and the secondary outcomes included adverse event frequency and remission/relapse at 4 years. The study showed no evidence to suggest that blocking and replacement is associated with improved outcomes compared to monotherapy [6].

The conventional treatment modalities for Graves' disease have remained unchanged for the past 70 years [7]. Recently, novel therapeutic agents targeting the CD40-CD154 co-stimulatory pathway or the insulin-like growth factor I receptor (IGF-IR) were developed [8]. Kahaly et al. [9] conducted an open-level phase II proof-of-concept study of iscalimab, an anti-CD40 monoclonal blocking antibody in 15 Graves' disease patients. Iscalimab induced euthyroid status in seven patients (47%) with a 12- to 20-week treatment period, but four (57%) of those patients relapsed after discontinuation. Twelve (80%) patients showed at least one reversible adverse event with a mild to moderate degree of severity [9]. The efficacy of the IGF-IR inhibitor teprotumumab on Graves' orbitopathy (GO), which is a serious extrathyroidal manifestation of Graves' disease associated with activation of the IGF-IR pathway [10], also showed promising results [11]; a 24-week treatment course of IGF-IR led to a reduction in proptosis (≥2 mm) in 78% of 41 patients versus 7% of 42 controls. It also resulted in better secondary outcomes with respect to the Clinical Activity Score (frequency of score 0–1: 59% vs. 21%), diplopia (response in 68% vs. 29%) and quality of life (GO-QOL overall score: 13.79 vs. 4.43) than placebo, with scarce adverse events [11].

RISK OF THYROID CANCER

The results from a population-based nested case-control study from Nordic population-based national cancer registry data (Denmark, Finland, Norway, and Sweden) were published in December 2020, demonstrating the impact of early-life risk exposures on the risk of thyroid cancer [12]. The thyroid cancer risk in offspring was analyzed in relation to maternal comorbidities and birth outcomes among 2,437 thyroid cancer cases (81.4% with papillary thyroid cancer [PTC], 77.1% women) matched with up to 10 non-cancer controls based on birth year, sex, and country, and county of birth. Postpartum outcomes (higher birth weight, congenital hypothyroidism, postpartum hemorrhage) and maternal comorbidities (diabetes before pregnancy, thyroid dysfunction, goiter, and benign thyroid neoplasms) were each associated with an increased risk of thyroid cancer in offspring. Of note, maternal thyroid comorbidity markedly increased the risk, with ORs of 67.36 (95% CI, 39.89 to 113.76) for goiter, 22.50 (95% CI, 6.93 to 73.06) for benign neoplasms, 18.12 (95% CI, 10.52 to 31.20) for hypothyroidism, and 11.91 (95% CI, 6.77 to 20.94) for hyperthyroidism. Fetal congenital hypothyroidism also showed high OR of 4.55 (95% CI, 1.58 to 13.08). This study provides evidence to support an association between intrauterine exposures, particularly those

related to maternal thyroid status during pregnancy, and later risk of thyroid cancer, although some genetic predisposition for thyroid disease could not be excluded.

Although, thyroid hormonal status is known to be associated with the risk of thyroid cancer, whether thyroid dysfunction plays a causal role in the development of cancer remains inconclusive. Tran et al. [13] provided additional evidence regarding that issue by demonstrating that both hyperthyroidism and hypothyroidism were associated with higher risks of thyroid cancer (pooled risk ratio, 4.49; 95% CI, 2.84 to 7.12 for hyperthyroidism) (pooled risk ratio, 3.31; 95% CI, 1.20 to 9.13 for hypothyroidism) as compared to euthyroidism in a meta-analysis of 13 million subjects from 15 studies. However, two recent results on the association of thyroid cancer with genetic variants related to thyroid function demonstrated contrary results. Zhou et al. [14] performed a genome-wide association study (GWAS) meta-analysis for 22.4 million genetic markers in up to 119,715 individuals from three famous studies—the Nord-Trøndelag Health Study (HUNT study), Michigan Genomics Initiative (MGI), and the ThyroidOmics consortium—and found 74 susceptible loci for TSH levels that explained 13.3% of its variance. Unexpectedly, phenome-wide association tests for the polygenic scores of the TSH variants showed an association between high TSH polygenic scores and low thyroid cancer risk, and two-sample Mendelian randomization analysis also suggested that the TSH variants associated with elevating levels could potentially reduce thyroid cancer risk in several independent populations. In a similarly designed GWAS meta-analysis in up to 72,167 European-descent individuals from the Breast Cancer Association Consortium and UK Biobank, Yuan et al. [15] showed that genetically predicted TSH levels (OR, 0.47; 95% CI, 0.30 to 0.73) and hypothyroidism (OR, 0.7; 95% CI, 0.51 to 0.98) were inversely associated with thyroid cancer. Although, these studies suggested that TSH and hypothyroidism may play a role in thyroid cancer, the causal relationship should be further elucidated in future studies.

DIAGNOSIS OF THYROID NODULES AND CANCER

The Bethesda classification defines the possibility of malignancy according to cytopathology findings derived from fine-needle aspiration for thyroid nodules [16]. Indeterminate cytology is a cumbersome category, with a difficult-to-define risk of cancer, and comprises approximately 20% of thyroid nodules. Recent molecular testing (gene panel tests) have been proposed to reduce the need for diagnostic lobectomy in patients with nodules with indeterminate cytology. Livhits et al. [17] investigated the effectiveness of molecular testing techniques, and in particular sought to determine whether an RNA test (Afirma genomic sequencing classifier) or a DNA-RNA test (ThyroSeq v3 multigene genomic classifier) offered superior performance in estimating the risk of malignancy of thyroid nodules with indeterminate cytology. In their randomized clinical trial of 346 patients with 372 indeterminate thyroid nodules, the prevalence of malignancy was 20%. The RNA test and the DNA-RNA test showed no statistically significant difference in performance, including sensitivity (100% vs. 97%, respectively), specificity (80% vs. 85%, respectively), and positive predictive value (53% vs. 63%) allowing half of patients with indeterminate nodules to avoid diagnostic surgery (51% vs. 49%, respectively).

Advanced computing and imaging techniques are also being applied to the diagnosis of thyroid nodules. A systematic review and meta-analysis of 19 studies involving 4,781 nodules evaluated the efficacy and accuracy of machine learning-based diagnosis [18]. The diagnostic performance of deep learning-based diagnosis was comparable to that of radiologists (sensitivity, 0.87 [95% CI, 0.78 to 0.93] vs. 0.87 [95% CI, 0.5 to 0.89]; specificity, 0.85 [95% CI, 0.76 to 0.91] vs. 0.87 [95% CI, 0.81 to 0.91]; diagnostic OR, 40.12 [95% CI, 15.58 to 103.33] vs. 44.88 [95% CI, 30.71 to 65.57]). Radiomics-assisted diagnosis based on ultrasound imaging of thyroid lesions adequately predicted the risk of lymph node metastasis in PTC [19]. Imaging data were collected by three ultrasound instruments (GE, SuperSonic, and Kretztechnik) and analyzed by four models with quantitative indexes (statistical model, traditional radiomics model, nontransfer learning radiomics and transfer learning radiomics [TLR]). The TLR model achieved an area under the curve of 0.95, indicating its accuracy for predicting in lymph node metastasis, and was validated in a different set from another hospital. By predicting the presence of neck lymph node metastasis, the TLR model can be applied to determine candidates for active surveillance of PTC [19].

NOVEL THERAPEUTICS FOR THYROID CANCER

Anaplastic thyroid carcinoma (ATC) remains one of the most aggressive and fatal solid tumors. Recently, a combination of dabrafenib and trametinib therapy demonstrated substantial survival improvement in patients harboring the *BRAF*^{V600E} variation [20]. Furthermore, neoadjuvant *BRAF*-directed therapy

showed the feasibility of complete resection and local disease control [21]. Based on these findings, the emerging use of targeted therapy, immunotherapy, surgery and radiation therapy might improve overall survival (OS) in patients with ATC [22]. In a single-institution (the University of Texas MD Anderson Cancer Center) cohort study of 479 patients with ATC over nearly 20 years, 1- and 2-year OS significantly increased from 35% and 18% in the 2000 to 2013 period to 47% and 25% in the 2014 to 2016 period, and 59% and 42% in the 2017 to 2019 period, respectively [23]. They found that a harmonious multidisciplinary approach could improve OS, with hazard ratios of 0.45 (95% CI, 0.39 to 0.63) for targeted therapy, 0.58 (95% CI, 0.36 to 0.94) for the addition of immunotherapy to targeted therapy, and 0.29 (95% CI, 0.10 to 0.78) for surgery following neoadjuvant *BRAF*-directed therapy. The last group (n=20) showed a 1-year survival of 94% with a median follow-up of 1.21 years. The researchers proposed a treatment algorithm for patients with ATC based on the staging and *BRAF* mutational status, and showed that preemptive genetic profiling and directed immunotherapy might lead to better treatment outcomes for patients with ATC, who are desperate due to the grave prognosis of the cancer.

Another disease entity that has lacked breakthrough therapies is radioactive iodine therapy-refractory differentiated thyroid cancer (DTC). Multikinase inhibitors targeting the growth factor signaling pathways (sorafenib and lenvatinib) were developed and approved as anti-cancer drugs for patients with advanced progressive DTC. Recently, novel target molecules including rearranged during transfection (RET), tropomyosin receptor kinase (TRK), and somatostatin receptors are emerging. The *RET* proto-oncogene encodes a transmembrane receptor tyrosine kinase that is constitutively activated in several types of cancers. Germline or somatic *RET* mutations were found in approximately 70% of medullar thyroid cancers, and *RET* fusions are found in fewer than 10% of DTC [24]. Selpercatinib, a selective RET inhibitor, proved its efficacy and safety in a phase 1–2 trial of 162 patients with *RET*-mutant medullary thyroid cancer (MTC) [24]. The response rate was 73% (95% CI, 62% to 82%) in 88 drug-naïve MTCs, and 69% (95% CI, 55% to 81%) and 79% (95% CI, 54% to 94%) in previously treated *RET*-mutant (n=55) and *RET*-fusion positive (n=17) MTCs, respectively. Selpercatinib showed durable efficacy with mainly low-grade toxic effects. The most common adverse event (grade 3 or higher) was hypertension, which was observed in 21% of patients. This study suggests that effective molecular screening for *RET* mutations will be essential in selecting proper patients.

The fusion of the *TRK* gene with another gene occurs in DTC and ATC, and activates carcinogenesis and promotes progression. There are two Food and Drug Administration-approved drugs for DTC patients: larotrectinib [25] and entrectinib [26]. Cabanillas et al. [27] analyzed data from 28 patients with advanced metastasis harboring neurotrophin tyrosine receptor kinase (*NTRK*) gene fusion pooled from two larotrectinib phase 1–2 clinical trials (NCT02122913 and NCT02576431). The objective response rate was 75% (95% CI, 55% to 89%) and the duration of response ranged from 1.9 to 41.0 months. Adverse events were mostly grade 1–2. These findings suggested that larotrectinib was highly efficacious and its safety profile was favorable. Entrectinib, another NTRK inhibitor, showed a response in one out of five patients with thyroid cancer in an integrated analysis of three phase 1–2 trials (ALKA-372–001, STARTRK-1, and STARTRK-2) [26].

Somatostatin receptor type 2 (SSTR2) is highly expressed in tumor tissues [28]. Thakur et al. [29] suggested that SSTR2 may function as a promising target molecule in thyroid cancer. SSTR2 was expressed more intensively in thyroid cancer lesions than in normal tissues, and a radiolabeled analog of SSTR2 (^{68}Ga-DOTA-TATE) showed higher uptake in thyroid cancer patients, particularly in Hürthle cell thyroid cancer resistant to radioactive iodine therapy. Treatment with ^{177}Lu-DOTA-EB-TATE, with higher theragnostic efficacy, reduced tumor size and extended survival in a mouse model. This novel radiolabeled analog of SSTR2 has the potential to be implicated in the treatment and diagnosis of resistant thyroid cancer.

THYROID DISEASE IN THE COVID-19 ERA

The outbreak of COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is causing overwhelming challenges for health systems [30]. Several retrospective reports have described the prevalence of thyroid-related diseases and investigated changes in treatment strategies as well as access to medical services. Lania et al. [31] analyzed thyroid function in 287 patients hospitalized with COVID-19 infection in a non-intensive care unit setting to determine whether this infection contributed to abnormalities in thyroid function. Seventy-three patients (25.4%) had thyroid dysfunction, including thyrotoxicosis in 58 patients and hypothyroidism in 15 patients. Low TSH levels were associated with high levels of the inflammatory cytokine interleukin-6, suggesting that COVID-19 may be associated with a high risk of thyrotoxicosis [31]. A similar study was also performed in China. Chen et al. [32] reported

that low TSH levels were present in 56% of patients with COVID-19. After recovery, the thyroid hormone levels of COVID-19 patients and control groups were not significantly different. Muller et al. [33] evaluated the frequency of subacute thyroiditis in COVID-19 patients requiring high intensity of care units (HICUs) or low intensity of care units (LICUs) as compared to non-COVID patients admitted to HICUs in Italy. Their study demonstrated that 93 COVID-19 patients in HICUs had lower TSH levels and higher C-reactive protein levels than non-COVID-19 patients in HICUs or COVID-19 patients in LICUs initially. Although more research is needed, these studies suggest that COVID-19 is associated with systemic immune activation that may possibly cause thyroid inflammation and result in hyperthyroidism or thyroiditis.

CONCLUSIONS

There have been rapid advances in understanding thyroid diseases in the last decades. This has been the result of breakthroughs in computational and genetic technology and the fruit of tremendous demands for personalized medicine. *Endocrinology and Metabolism* looks forward to publishing excellent and promising results in this field in 2021.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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