Advancements in Clinical Thyroidology in 2016

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In this article, we summarize the seminal highlights of clinical thyroidology literature published in 2016. The main focus of these articles were thyroid nodules, thyroid cancer, cubclinical hypothyroidism in pregnancy, Graves' disease in pregnancy, the American Thyroid Association guidelines for adult patients with thyroid nodules and differentiated thyroid cancer, and the American Thyroid Association guidelines for the diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis.

Keywords

Fine needle aspiration, noninvasive follicular thyroid neoplasm with papillary-like nuclear features, tyrosine kinase inhibitor, radiofrequency ablation, ethanol ablation, propylthiouracil

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The year 2016 has been an exciting one in the world of thyroid disease, marking a new era for both research and clinical management. As a subspecialty, we are continuously re-evaluating not only our current treatment strategies, but also our classification of disease, right down to adjusting the nomenclature. All of this has occurred within the last year and the impact of many of these changes is requiring clinical endocrinologists to make significant changes in their approach to patient care. Here, we summarize some of the advancements that have clinical relevance.

Not surprisingly, in 2016 the majority of the literature explored thyroid nodules and thyroid cancer.[1] We began the year with the publication of the latest American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer.[2] In agreement with the review by Kim et al.,[3] at the heart of these new guidelines is the indication that we should be doing much less in management and treatment, but with under the premise that patients are thoroughly and appropriately assessed.

Highlighting this approach are the recommendations to hold the standard for diagnostic fine needle aspiration (FNA) to the most detailed sonographic characteristics of these nodules, eliminating the >5 mm threshold to FNA for high-risk individuals and suggesting that observing sonographically very low risk nodules without FNA is also a reasonable option, no matter how large the lesion. Although highly suspicious thyroid nodules with a benign cytology should have a repeat FNA within a year, it is now recommended that in very low suspicion nodules we should consider discontinuing surveillance altogether after two benign FNA results.

These guidelines have also, at last, added the recommendation of thyroid lobectomy for low-risk thyroid cancer patients with tumors of 1–4 cm in size and strongly recommend lobectomy for sub centimeter thyroid nodules, which can also be closely monitored without surgery as an alternative. Last, but not least, the threshold for administering radioactive iodine (RAI) has been increased significantly, and the routine use of recombinant human thyroid stimulating hormone stimulated thyroglobulin levels has been discouraged in low-risk situations.

So, are these guidelines an advancement? The authors should be congratulated for another monumental task and excellent review of the current thyroid nodule and cancer literature. They certainly correct some points from the previous version, but they appear to some of us to err too much on the side of doing nothing. Discontinuing surveillance of nodular thyroids and just providing surveillance for small thyroid cancers remain controversial suggestions. Of course, if only everyone would stop doing FNAs on small nodules then this situation would not need to be discussed. But as long as fee-for-service in the US continues, we can be sure that such patients will continue to present for advice on future management.

Also this year, there have been multiple articles suggesting a nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma, which have reached major news media.[4] The recommended name for this pathology is now "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP).[5–8] Note the removal of the term 'carcinoma'. This was a result of an extensive consensus review of a multitude of patients who have had prolonged follow-up after lobectomies with no RAI. They had a recurrence rate of <1%. It is estimated that this new classification may impact >45,000 patients per year worldwide, and will lead to less extensive surgery and a further decrease in RAI use.

Lenvatinib, a novel tyrosine kinase inhibitor (TKI), which was approved by both the US Food and Drug Administration and the European Medicines Agency in 2015 for the treatment progressive, radioiodine refractory differentiated thyroid cancer, was definitely in the spotlight this year, with continued positive reports of increased progression-free survival (PFS) rates showing it to be the most promising salvage therapy available for use even in patients who have been treated with another TKI previously.[9–11] Nevertheless, an increased long-term survival rate has yet to be demonstrated and the drug side effects can be unpleasant.

A systematic review and meta-analysis on the safety and efficacy of radiofrequency ablation (RFA) and ethanol ablation (EA) for treating local recurrence of thyroid cancer,[12] showed significant reductions in serum thyroglobulin levels and low complication rates, suggesting this modality may be an alternative to surgical re-intervention. Previous cases using these approaches with benign nodules and cysts have been reported, with some success[13,14] but their use in malignant disease may be most useful when surgery is not a good option. A similar approach has been used for parathyroid lesions.[15]

The debate on subclinical hypothyroidism and pregnancy continues, with over 30 articles published on the subject in 2016. This year, some fairly strong prospective data indicated that subclinical hypothyroidism is not associated with fecundity, pregnancy loss or fewer live births,[16] yet there were other reports signaling adverse pregnancy outcomes.[17–19] Although a retrospective study suggested that treatment may be of benefit,[20] we do not yet have a definitive answer from a large randomized trial. Of note, a study looking at euthyroid women with positive thyroid antibodies found no difference in the rate of miscarriage when treated with levothyroxine.[21]

In line with last year's meta-analysis of immunosuppressive monotherapy for Graves' orbitopathy,[22] a meta-analysis looking at the reduction in the relapse rate of Graves' Disease with immunosuppressive treatment in addition to standard antithyroid therapy was published this year.[23] This is the first systematic review and meta-analysis focusing on this endpoint, and although the studies reviewed were small, results were very positive favoring immunosuppressive therapy, which may be a promising treatment option in the near future. The surprisingly good results from the use of CellCept in Graves' orbitopathy[24] are exciting but need further confirmation.

In addition, the American Thyroid Association developed new guidelines for the diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis this year.[25] In contrast to the thyroid nodule and differentiated thyroid cancer guidelines, however, few changes have been made. Noteworthy are the recommendations to treat postoperative hypocalcemia empirically and/or prophylactically in high-risk Graves' disease patients undergoing total thyroidectomy, the official institution of the Burch-Wartofsky Point Scale and Japanese Thyroid Association categories for thyroid storm management, instituting thyroid sonography as a standard preoperative test in patients undergoing lobectomy for Toxic Adenoma, and a timing adjustment in the surveillance of thyrotropin receptor autoantibodies during pregnancy.

Finally, the treatment of pregnant patients who have Graves' disease has continued to be surrounded by controversy. It is clear that methimazole is associated with a rare embryopathy but recent information also indicates that PTU is associated with congenital abnormalities, although of less severity.[26] Therefore, it is best to avoid antithyroid drugs as much as possible in women who are planning pregnancy since it is likely they will not come to attention until they are eight weeks pregnant and have already passed the most vulnerable stage of fetal development. Resisting the urge to prescribe such drugs to only mildly hyperthyroid pregnant women would seem the most sensible approach, letting the immunosuppression of pregnancy take over.[27] ❑

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The Decade in Clinical Thyroid Disease: An Analysis of Published Literature

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Background: The purpose of this study was to assess the current status of the clinical thyroidology literature using bibliographic analysis.
Methods: The subject ''clinical thyroidology'' was divided into six broad topics: iodine deficiency/iodine nutrition, hypothyroidism, hyperthyroidism/thyrotoxicosis, thyroiditis/autoimmune thyroid disease, thyroid nodules/multinodular goiter, and thyroid cancer. Using Scopus, an online bibliographic searching tool, this study sought to examine the trends in the publication of clinical thyroid disease–related research articles over the decade from 2006 through the end of 2015. Citation counts were also retrieved for individual research papers in order to find papers that might have had a bigger impact on clinical practice. Review articles, guidelines, and editorials were excluded.
Results: A total of 19,055 articles were published in the broad area of clinical thyroid disease. The largest proportion was in the topic of thyroid cancer, accounting for >30% of the total. The numbers of papers published annually on thyroid nodules and thyroid cancer increased progressively over the decade. The largest proportion of clinical thyroid publications emanated from the United States, and the majority of papers were published in subspecialty journals. Within each clinical thyroid topic, the most highly cited papers published from 2006 to 2015 were identified, and outliers—that is, papers that had been cited far more often that others in the topic—were also identified. The most highly cited paper in all of clinical thyroidology was a 2006 study describing the increase in thyroid cancer incidence in the United States (*JAMA* 295:2164–2167). Most of the highly cited clinical papers were case series or cohort studies, rather than randomized controlled trials.
Conclusions: The number of papers in clinical thyroid disease is expanding rapidly, with >1000 papers published annually over the last decade. Research papers on thyroid nodules and cancer accounted for 51% of all clinical thyroid disease–related papers. More randomized controlled trials have been published in the last few years, portending a bright future for clinical thyroidology.

Introduction

As with all scientific and medical disciplines, there have been dramatic advances in the prevention, diagnosis, and treatment of thyroid disease over the last several decades. The purpose of the research presented in this paper is to quantify the recent progress within the realm of clinical thyroidology using publication and citation analysis. By analyzing the number of scientific publications that have appeared over a specific time interval (the last decade), as well as the frequency with which specific publications have been cited in the literature, this study aims to provide insights into how clinical thyroidology is evolving. These data may enable the forces that are driving these temporal changes to be better understood, and may help stakeholders to develop strategies to reverse apparently declining interest in some areas, as well as help researchers to capitalize on those areas that appear to be growing in interest and importance.

Methods

Elsevier's Scopus database was used for this analysis. Scopus is a web-based tool developed for bibliographic analysis. It was selected because it reports on the country of the affiliation of the authors of papers, as well as other details, including institutions where research was done. Scopus includes >18,000 journal titles in medicine, nursing, veterinary medicine, dentistry, and multidisciplinary health professions, including all of Medline (http://hlwiki.slais.ubc.ca/index.php/Scopus). Twenty-one percent of journals are in languages other than English, and >50% of the titles originate outside of North America (www.elsevier.com/solutions/scopus). The

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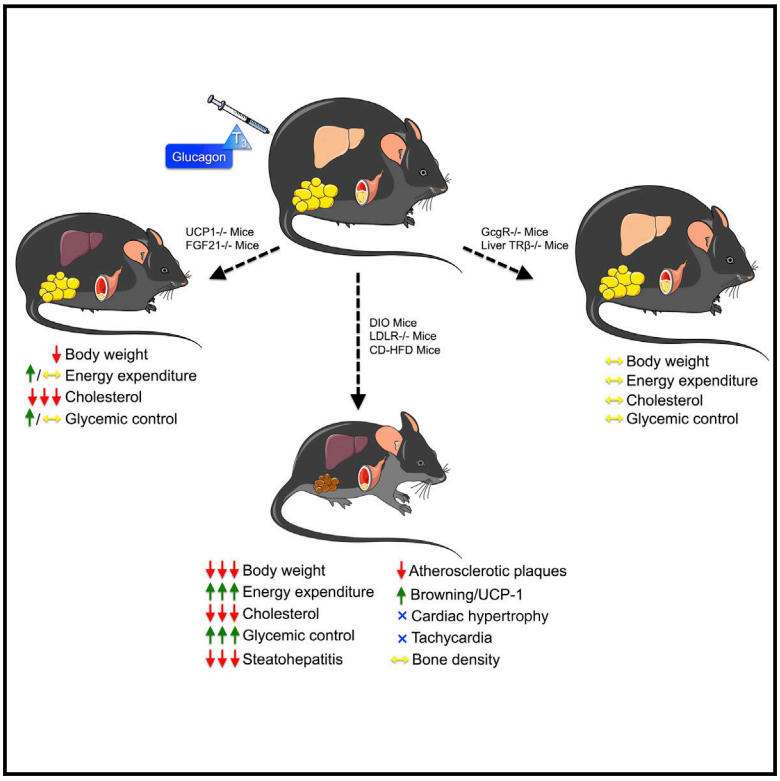
Article

Cell

Chemical Hybridization of Glucagon and Thyroid Hormone Optimizes Therapeutic Impact for Metabolic Disease

Graphical Abstract



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In Brief

The therapeutic benefits of two hormones are maximized in a synthetic hybrid molecule that treats metabolic syndrome in mice by synergizing favorable effects and off-setting liabilities.

Highlights

- Glucagon/T_3 corrects dyslipidemia, obesity, and hyperglycemia in DIO mice
- Glucagon/T_3 improves NASH and atherosclerosis in preclinical disease models
- Precise delivery of T_3 to the liver mediates benefits and spares cardiac toxicity
- Hepatic T_3 action counteracts the diabetogenic liability of glucagon

Data Resources

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ORIGINAL ARTICLE

Liothyronine use in a 17 year observational population-based study - the tears study

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Abstract

Objective To look at adverse outcomes for patients on liothyronine compared to l-thyroxine. Some trials have examined the relative merits of liothyronine but none have looked at adverse outcomes in large numbers.

Study Design An observational study of all patients prescribed thyroid hormone replacement in Tayside Scotland (population 400 000) from 1997 to 2014.

Patients A study group of patients having ever used liothyronine ($n = 400$) was compared to those who had only used l-thyroxine ($n = 33\ 955$). All patients were followed up until end-point, death or leaving Tayside.

Measurements Mortality rates and admissions with cardiovascular disease, atrial fibrillation, fractures, breast cancer and mental diseases were compared. Incident use of bisphosphonates, statins, antidepressants and antipsychotics was compared.

Results Compared to patients only taking l-thyroxine, those using liothyronine had no increased risk of cardiovascular disease [hazard ratio (HR) 1·04; 95% CI 0·70–1·54], atrial fibrillation (HR 0·91: 0·47–1·75), or fractures (HR 0·79: 0·49–1·27) after adjusting for age. There was no difference in the number of prescriptions for bisphosphonates or statins. There was an increased risk of new prescriptions for antipsychotic medication (HR 2·26: 1·64–3·11 $P < 0·0001$) which was proportional to the number of liothyronine prescriptions. There was a non-significant trend towards an increase in breast cancer and new use of antidepressant medications. During follow-up, median TSH was higher for patients on l-thyroxine alone (2·08 *vs* 1·07 mU/L; $P < 0·001$).

Conclusion For patients taking long-term liothyronine we did not identify any additional risk of atrial fibrillation, cardiovascular disease or fractures. There was an increased incident use of antipsychotic medication during follow-up.

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Introduction

Hypothyroidism affects around 5% of the population and the recommended treatment is l-thyroxine.[1,2] Patients usually respond well to treatment with l-thyroxine, and the dose is monitored in response to a combination of patients' symptoms and serum TSH concentrations. However, some patients describe ongoing adverse symptoms despite being on what seem adequate doses of l-thyroxine, even with serum TSH concentrations towards the lower end of the reference range.[3]

The thyroid gland secretes some tri-iodothyronine, and tri-iodothyronine is the main active hormone at cellular level, converted from thyroxine by intracellular deiodinases. Liothyronine is a drug that is identical to the hormone tri-iodothyronine. As a result a number of trials have been conducted assessing the efficacy of combined l-thyroxine with liothyronine therapy, to see if the combination is better than l-thyroxine alone. Of 12 trials, two showed a significant improvement,[4,5] two a minor improvement[3,6] and eight showed no improvement[7–14] in quality of life scores. In seven trials focussing on changes in thyroid related symptoms, no improvements were observed in the combination therapy group[3,7,8,11–13,15] However, it is possible that there is a subgroup of patients who do benefit. Genetic differences determining activity of the deiodinase gene impacting on serum TSH concentrations have been identified in some[16] but not all studies.[17] However, these results give grounds for an as yet unproven hypothesis that there may be subgroups of patients who may metabolise thyroxine differently, and could possibly benefit from combination therapy.

Given a free choice, patients preferred combination therapy in the majority of trials.[4,5,9,11,13] Although these trials had small numbers, this may hint at some improved outcomes that were not identified in more detailed analyses. However, there was no difference in patient preference in the larger trials,[3,8] although serum TSH was higher in the patients taking combination therapy in one of these trials,[8] which may have reduced any potential benefit.

Thyroid Function and Cancer Risk: The Rotterdam Study

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Context: In vitro and in vivo experiments have assigned both oncosuppressive and oncogenic properties to thyroid hormones. Population-based studies have found inconclusive results.

Objective: We aimed to prospectively assess the relation between thyroid function and incident cancer in a population-based setting.

Design, Setting, and Participants: The current study is a prospective population-based cohort study including 10 318 participants for whom baseline measurements of free T_4 (FT_4) and/or TSH were available.

Main Outcome Measures: Cox proportional hazards models were used to assess hazard ratios (HRs) of any solid non-skin cancer, as well as lung, breast, prostate, and gastrointestinal cancer specifically.

Results: Higher FT_4 levels were associated with a higher risk of any solid cancer (HR, 1.42; 95% confidence interval [CI], 1.12–1.79), lung cancer (HR, 2.33; 95% CI, 1.39–3.92) and breast (HR, 1.77; 95% CI, 1.10–2.84) cancer. The risk estimates were similar after exclusion of thyroid-altering medication, but the association lost significance for breast cancer. Compared with the lowest FT_4 tertile, the highest tertile was associated with a 1.13-fold increased risk of any solid, 1.79-fold increased risk of lung, and 1.14-fold increased risk of breast cancer (*P* for trend $<.05$ for all). For TSH levels we found no associations with cancer risk. There was no differential effect of sex or age on the association between thyroid function and cancer risk.

Conclusions: Higher FT_4 levels are significantly associated with an increased risk of any solid, lung, and breast cancer. Further research should elucidate the underlying pathophysiological mechanisms. **(*J Clin Endocrinol Metab* 101: 5030–5036, 2016)**

Thyroid hormone plays an important role in growth, differentiation, development and metabolism. Via binding to nuclear thyroid hormone receptors (TRs), thyroid hormone can induce or inhibit gene transcription (1, 2). Many pathways influenced by thyroid hormone also play a role in tumorigenesis. For example, induction of deiodinase 3, a thyroid hormone-inactivating enzyme, sustains proliferation in colon carcinoma, suggesting a link between local hypothyroidism and tumor growth (3). In addition, it has been demonstrated that thyroid hor-

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Abbreviations: BMI, body mass index; CI, confidence interval; FT4, free T_4; GI, gastrointestinal; HIF1, hypoxia-inducible factor 1; HR, hazard ratio; IQR, interquartile range; PALGA, Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief; *PD-L1*, programmed death-ligand 1; PI3K, phosphatidylinositol-3-kinase; RS, Rotterdam Study cohort; SES, socioeconomic status; TR, thyroid hormone receptor.

Hypothyroidism and hyperthyroidism and breast cancer risk: a nationwide cohort study

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Abstract

Objective: The association between thyroid disease and breast cancer risk remains unclear. We, therefore examined the association between hypothyroidism, hyperthyroidism and breast cancer risk.
Design: This was a population-based cohort study.
Methods: Using nationwide registries, we identified all women in Denmark with a first-time hospital diagnosis of hypothyroidism or hyperthyroidism, 1978–2013. We estimated the excess risk of breast cancer among patients with hypothyroidism or hyperthyroidism compared with the expected risk in the general population, using standardized incidence ratios (SIRs) as a measure of risk ratio. Breast cancer diagnoses in the first 12 months following diagnosis of thyroid disease were excluded from the calculations to avoid diagnostic work-up bias.
Results: We included 61 873 women diagnosed with hypothyroidism and 80 343 women diagnosed with hyperthyroidism. Median follow-up time was 4.9 years (interquartile range (IQR): 1.8–9.5 years) for hypothyroidism and 7.4 years (IQR: 3.1–13.5 years) for hyperthyroidism. Hyperthyroidism was associated with a slightly increased breast cancer risk compared with the general population (SIR: 1.11, 95% CI: 1.07–1.16), which persisted beyond 5 years of follow-up (SIR: 1.13, 95% CI: 1.08–1.19). In comparison, hypothyroidism was associated with a slightly lower risk of breast cancer (SIR: 0.94, 95% CI: 0.88–1.00). Stratification by cancer stage at diagnosis, estrogen receptor status, age, comorbidity, history of alcohol-related disease and clinical diagnoses of obesity produced little change in cancer risk.
Conclusions: We found an increased risk of breast cancer in women with hyperthyroidism and a slightly decreased risk in women with hypothyroidism indicating an association between thyroid function level and breast cancer risk.

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Introduction

Breast cancer is the most frequent cancer in females, with 458 337 new cases diagnosed in Europe in 2012 (1). Endogenous and exogenous sex hormones play an important role in the etiology of breast cancer (2). *In vitro*, high levels of thyroid hormones have estrogen-like effects (3, 4), promoting breast cancer cell proliferation (5, 6) and stimulating angiogenesis (7). Therefore, hyperthyroidism, characterized by increased levels of thyroid hormones, may potentially also increase breast cancer risk.

Epidemiological evidence concerning thyroid disorders and breast cancer risk remains unclear. Some epidemiological studies have reported increased risks associated with hypothyroidism (8, 9), hyperthyroidism (10, 11, 12), goiter (13) and thyroid autoimmune diseases (14, 15), while others have found no association (9, 16, 17, 18). Only four studies employed a cohort design (9, 11, 12, 15); in case–control studies, reverse causation is a plausible competing explanation since breast cancer or its treatment may affect thyroid hormone levels (19). Moreover, some studies have not distinguished between hypothyroidism and hyperthyroidism, despite their contrasting hormonal profiles (13, 16, 17). We conducted a

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Thyroid Hormone, Cancer, and Apoptosis

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ABSTRACT

Thyroid hormones play important roles in regulating normal metabolism, development, and growth. They also stimulate cancer cell proliferation. Their metabolic and developmental effects and growth effects in normal tissues are mediated primarily by nuclear hormone receptors. A cell surface receptor for the hormone on integrin αvβ3 is the initiation site for effects on tumor cells. Clinical hypothyroidism may retard cancer growth, and hyperthyroidism was recently linked to the prevalence of certain cancers. Local levels of thyroid hormones are controlled through activation and deactivation of iodothyronine deiodinases in different organs. The relative activities of different deiodinases that exist in tissues or organs also affect the progression and development of specific types of cancers. In this review, the effects of thyroid hormone on signaling pathways in breast, brain, liver, thyroid, and colon cancers are discussed. The importance of nuclear thyroid hormone receptor isoforms and of the hormone receptor on the extracellular domain of integrin αvβ3 as potential cancer risk factors and therapeutic targets are addressed. We analyze the intracellular signaling pathways activated by thyroid hormones in cancer progression in hyperthyroidism or at physiological concentrations in the euthyroid state. Determining how to utilize the deaminated thyroid hormone analog (tetrac), and its nanoparticulate derivative to reduce risks of cancer progression, enhance therapeutic outcomes, and prevent cancer recurrence is also deliberated. © 2016 American Physiological Society. *Compr Physiol* 6:1221-1237, 2016.

Introduction

Thyroid hormones (THs) are iodinated endogenous compounds known to regulate a wide range of cellular activities through thyroid hormone receptors (TRs). Thyroid hormones, such as L-thyroxine (T_4), are major secretory products of a normal thyroid gland. Although T_4 has certain physiological roles—for example, in the actin cytoskeleton (52) and angiogenesis (14, 112)—its principal function is thought to be that of a prohormone, undergoing conversion to 3,5,3′-triiodo-L-thyronine (T_3) by deiodination to effect genomic hormonal actions that require nuclear receptors for thyroid hormone receptors (17). Nuclear receptors are sequence-specific ligand-dependent transcription factors that trigger many of the downstream effects of thyroid hormones, such as T_3, by activating or repressing target genes. THs are critical to organism development, tissue differentiation and growth, and maintenance of a cell's metabolic balance (169). These actions are thyroid hormone receptor dependent. Severe disruption of THs actions during fetal and early neonatal development leads to permanent functional deficits (53), particularly of the nervous system.

Integrins are heterodimeric structural components of plasma membranes that are able to bind to a large number of extracellular matrix (ECM) proteins as ligands. Certain ones of these ligands contain Arg-Gly-Asp (RGD) sequences that allow recognition of ECM proteins by a group of specific integrins and permit integrins to generate intracellular (outside-in) signals specific to ECM molecules (38). In addition to protein ligands, integrin αvβ3 was shown to have small-molecule receptor sites for thyroid hormones and hormone analogs, dihydrotestosterone, and resveratrol, a polyphenol with certain estrogen-like features. These binding sites are close to the RGD recognition site on αvβ3. The TH receptor contains discrete binding domains, one of which binds both T_4 and T_3, and the other is specific for T_3; the two sites have discrete functions with regard to regulating signal transduction pathways and cell functions (32, 101) (see later).

In dividing endothelial cells and tumor cells, the plasma membrane expresses large amounts of integrin αvβ3, the extracellular domain of which bears the thyroid hormone

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Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

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IMPORTANCE Although growing evidence points to highly indolent behavior of encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), most patients with EFVPTC are treated as having conventional thyroid cancer.

OBJECTIVE To evaluate clinical outcomes, refine diagnostic criteria, and develop a nomenclature that appropriately reflects the biological and clinical characteristics of EFVPTC.

DESIGN, SETTING, AND PARTICIPANTS International, multidisciplinary, retrospective study of patients with thyroid nodules diagnosed as EFVPTC, including 109 patients with noninvasive EFVPTC observed for 10 to 26 years and 101 patients with invasive EFVPTC observed for 1 to 18 years. Review of digitized histologic slides collected at 13 sites in 5 countries by 24 thyroid pathologists from 7 countries. A series of teleconferences and a face-to-face conference were used to establish consensus diagnostic criteria and develop new nomenclature.

MAIN OUTCOMES AND MEASURES Frequency of adverse outcomes, including death from disease, distant or locoregional metastases, and structural or biochemical recurrence, in patients with noninvasive and invasive EFVPTC diagnosed on the basis of a set of reproducible histopathologic criteria.

RESULTS Consensus diagnostic criteria for EFVPTC were developed by 24 thyroid pathologists. All of the 109 patients with noninvasive EFVPTC (67 treated with only lobectomy, none received radioactive iodine ablation) were alive with no evidence of disease at final follow-up (median [range], 13 [10-26] years). An adverse event was seen in 12 of 101 (12%) of the cases of invasive EFVPTC, including 5 patients developing distant metastases, 2 of whom died of disease. Based on the outcome information for noninvasive EFVPTC, the name "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) was adopted. A simplified diagnostic nuclear scoring scheme was developed and validated, yielding a sensitivity of 98.6% (95% CI, 96.3%-99.4%), specificity of 90.1% (95% CI, 86.0%-93.1%), and overall classification accuracy of 94.3% (95% CI, 92.1%-96.0%) for NIFTP.

CONCLUSIONS AND RELEVANCE Thyroid tumors currently diagnosed as noninvasive EFVPTC have a very low risk of adverse outcome and should be termed NIFTP. This reclassification will affect a large population of patients worldwide and result in a significant reduction in psychological and clinical consequences associated with the diagnosis of cancer.

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RESEARCH ARTICLE

Impact of Reclassification on Thyroid Nodules with Architectural Atypia: From Non-Invasive Encapsulated Follicular Variant Papillary Thyroid Carcinomas to Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features

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Abstract

Background

The follicular variant of papillary thyroid cancer (FVPTC), especially the encapsulated non-invasive subtype, is a controversial entity. Recent study suggested using 'non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)' for these indolent carcinomas. We evaluated the impact of reclassification from non-invasive encapsulated FVPTCs (EFVPTCs) to NIFTPs in the diagnosis of thyroid nodules with architectural atypia.

Methods

We reviewed 1301 thyroid nodules with architectural atypia in core needle biopsy (CNB) specimens obtained from March 2012 to February 2013. Nodules were classified into atypia of undetermined significance with architectural atypia (AUS-A, 984, 76%) or follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN, 317, 24%). Among them, diagnostic surgery was performed in 384 nodules (30%).

Results

In total, 160 nodules (42%) presented final malignant diagnoses including 39 non-invasive encapsulated FVPTCs (10%). The malignancy rate was estimated to be 7–35% in AUS-A nodules and 28–49% in FN/SFN nodules. After reclassification, the malignancy rate was much decreased and estimated to be 5–24% in AUS-A nodules, and 23–39% in FN/SFN

Competing Interests: The authors have declared that no competing interests exist.

nodules. Thyroid nodules with final malignant diagnoses were significantly more likely to have a FN/SFN CNB diagnosis, malignant US features and concomitant nuclear atypia in CNB specimens. However, these factors could not differentiate NIFTPs from other malignancies.

Conclusions

After reclassification of non-invasive EFVPTCs to NIFTPs, the malignancy rate of thyroid nodules with architectural atypia in CNB specimens was decreased. However, there were no preoperative factors differentiating other malignancies from NIFTPs. The presence of malignant US features or concomitant nuclear atypia might help clinicians deciding diagnostic surgery but, these features also might indicate NIFTPs.

Introduction

The follicular variant of papillary thyroid cancer (FVPTC) is a one common subtype of thyroid cancer. There are two main subtypes of FVPTCs: infiltrative and encapsulated. FVPTC, especially the encapsulated non-invasive subtype, is a controversial entity with low inter-observer reproducibility, and only small percentages of these tumors are reported to show aggressive clinical behavior [1]. Because of the clinically indolent nature of non-invasive encapsulated FVPTCs (EFVPTCs), there was a suggestion that these tumors should no longer be termed as carcinomas, but be diagnosed using an alternative term, a non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [1–3].

FVPTCs show both architectural atypia of neoplastic microfollicular proliferation more than 50% and nuclear atypia of papillary thyroid cancer with variable degree in diagnostic specimens and most of them resulted in indeterminate diagnostic categories in the thyroid fine needle aspiration biopsies [3] or core needle biopsy (CNB) specimens.

In this study, we evaluated the final pathologic diagnoses of thyroid nodules with indeterminate results, especially with architectural atypia, in CNB specimens. We aimed to analyze the changes in the malignancy rates of thyroid nodules with architectural atypia after reclassification of non-invasive EFVPTCs to NIFTPs. We also tried to find preoperative factors predicting final diagnoses of these nodules.

Methods

Thyroid nodules and patients

From March 2012 to February 2013, 3376 thyroid nodules were evaluated by US-guided CNB at the Asan Medical Center (Seoul, Korea). We excluded nodules evaluated with repeated CNB during the study period. Among the assessed thyroid nodules, 1301 (39%) presented with architectural atypia in the CNB specimens. We retrospectively reviewed the clinicopathological characteristics of these 1301 thyroid nodules and the patients. This study was approved by our institutional review board (2015–0905). Informed consent was waived due to the retrospective nature of this study and anonymized medical records were used for analysis.

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Preoperative Cytologic Diagnosis of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features: A Prospective Analysis

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Background: The term noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has been proposed to replace noninvasive follicular variant of papillary thyroid carcinoma (FVPTC) in recognition of the indolent behavior of this tumor. The ability to differentiate NIFTP from classical papillary thyroid carcinoma (cPTC) by fine-needle aspiration (FNA) would facilitate conservative management for NIFTP. The aim of this study was to determine if NIFTP can be distinguished prospectively from cPTC.
Methods: From June 2015 to January 2016, thyroid FNAs with a diagnosis of ''malignant'' or ''suspicious for malignancy'' were prospectively scored for features associated with NIFTP/FVPTC (microfollicular architecture) or cPTC (papillae, psammomatous calcifications, sheet-like architecture, and nuclear pseudoinclusions) and categorized as NIFTP/FVPTC, cPTC, or indeterminate. Results were correlated with subsequent histologic diagnoses.
Results: The study included 52 patients with 56 resected nodules with a cytologic diagnosis of ''malignant'' (43/56) or ''suspicious for malignancy'' (13/56). Forty-nine patients (94%) underwent initial total thyroidectomy. Histopathologic diagnoses included 42 cPTC, 8 NIFTP, 3 invasive FVPTC, 2 follicular adenomas, and 1 poorly differentiated carcinoma. Excluding 7 indeterminate cases, 89% (8/9) of nodules classified as NIFTP/FVPTC on FNA demonstrated follicular-patterned lesions on histology (5 NIFTP, 1 invasive FVPTC, 2 follicular adenomas). Cytopathologists prospectively identified cPTC in 95% (38/40) of cases.
Conclusions: In thyroid FNAs with cytologic features concerning for PTC, NIFTP/FVPTC can be distinguished from cPTC in most cases by assessing a limited number of features. Therefore, it is both feasible and appropriate to attempt to separate NIFTP/FVPTC from cPTC on FNA to promote appropriate clinical management.

Introduction

The term noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has recently been proposed to replace noninvasive follicular variant of papillary thyroid carcinoma (FVPTC) (1). The designation of NIFTP rather than carcinoma represents a culmination of work demonstrating that these tumors are a distinct subset of FVPTC with a very indolent clinical course (2–5). The histologic diagnosis of NIFTP relies on a few critical morphologic criteria, including (1) the presence of an entirely follicular architecture with <1% papillary structures, (2) the nuclear features of PTC including fine chromatin, pale nuclei, and nuclear grooves, (3) a sharp interface between the tumor and the adjacent thyroid parenchyma, including encapsulated, partially-encapsulated, and well-circumscribed tumors, and (4) the lack of infiltrative growth, capsular invasion, or lymphovascular invasion. Accordingly, NIFTP warrants excision by lobectomy to exclude an invasive FVPTC, classical PTC (cPTC), or other thyroid malignancy, and because NIFTP itself requires excision since it may be a precursor to a more aggressive thyroid tumor. Once the diagnosis of NIFTP is made histologically, however, further therapy such as completion thyroidectomy and/or radioiodine therapy may not be warranted.

Adoption of the NIFTP terminology has significant consequences for thyroid fine-needle aspiration (FNA). The risk of malignancy, assuming NIFTP is classified as nonmalignant, associated with all diagnostic categories of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) would decrease. Of particular note, our group demonstrated

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The Ethical Implications of the Reclassification of Noninvasive Follicular Variant Papillary Thyroid Carcinoma

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Background: Several studies have highlighted the lack of consensus in the diagnosis of follicular variant of papillary thyroid carcinoma (FVPTC). An international multidisciplinary panel to address the controversy was assembled at the annual meeting of the Endocrine Pathology Society in March of 2015, leading to the recent publication reclassifying encapsulated (or noninvasive) FVPTC (EFVPTC) as a benign neoplasm. Does this change in histologic taxonomy warrant a change in clinical practice, and how should it affect those who have been given this diagnosis in the past? We consider the financial and psychological impact of this reclassification and discuss the ethical, legal, and practical issues involved with sharing this information with the patients who are affected.

Summary: The total direct and indirect cost of thyroid cancer surveillance in patients is significant. High levels of clinically relevant distress affect up to 43% of patients with papillary thyroid carcinoma, as estimated by the Distress Thermometer developed by the National Comprehensive Cancer Network for detecting distress in cancer patients. Although there are currently no legal opinions that establish a precedent for recontacting patients whose clinical status is altered by a change in nomenclature, the prudent course would be to attend to the requirements of medical ethics.

Conclusion: Informing patients with a previous diagnosis of EFVPTC that the disease has been reclassified as benign is expected to have a dramatic effect on their surveillance needs and to alleviate the psychological impact of living with a diagnosis of cancer. It is important to re-evaluate the pathologic slides of those patients at risk to ensure that the invasive nature of the tumor is comprehensively evaluated before notifying a patient of a change in diagnosis. The availability of the entire tumor for evaluation of the capsule may prove to be a challenge for a portion of the population at risk. We believe that it is the clinician's professional duty to make a sincere and reasonable effort to convey the information to the affected patients. We also believe that the cost savings with respect to the need for additional surgery, radioactive iodine, and rigorous surveillance associated with a misinterpretation of the biology of the diagnosis of EFVPTC in less experienced hands will likely more than offset the cost incurred in histologic review and patient notification.

Introduction

The diagnosis of follicular-pattern lesions showing nuclear features of papillary thyroid carcinoma (PTC) is challenging and has been the subject of much debate over the last 50 years (1). Several papers have highlighted the lack of consensus in the diagnosis of follicular variant of papillary thyroid carcinoma (FVPTC) even by pathologists who are experts in interpreting thyroid cancer histology (2). Lloyd *et al.* (3) reported 87 cases of FVPTC that were reviewed by 10 thyroid pathology experts with a 39% cumulative frequency of diagnostic concordance. Owing to the lack of diagnostic agreement, treatment guidelines and prognosis for individuals with these thyroid lesions are varied. The challenge is that the minimal histological criteria for the diagnosis of FVPTC, particularly in encapsulated neoplasms, are subjective. The clinical behavior of FVPTC with an invasive growth pattern is different from its encapsulated noninvasive counterpart (4). The metastatic potential of encapsulated, also known as noninvasive, FVPTCs has been cited as

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EDITORIAL

Why the European Association of Nuclear Medicine has declined to endorse the 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer

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Keywords Thyroid cancer · American Thyroid Association · Management guidelines

Recently the American Thyroid Association (ATA) released the third version of one of the most cited differentiated thyroid cancer (DTC) guidelines under the title "2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer" [1]. Compared to the earlier versions [2, 3], these guidelines are a major departure, as the volume of the text, the number of recommendations and the number of references have increased considerably.

We fully understand the effort involving many hours of work that must have been required for the rigorous screening of the literature to produce the evidence tables and the eventual definitions of the recommendations. The document consists of roughly 73,000 words which make up the 101 recommendations and the explanatory text and comments. In the current ATA guidelines, most of the text appears eminently sensible and represents a significant advance from previous DTC-related guidelines published by the ATA as well as other societies, including the 2008 European Association of Nuclear Medicine (EANM) guidelines on ^{131}I therapy of DTC [4–7]. For instance, we welcome the clear division of indications for initial ^{131}I treatment of DTC patients after total thyroidectomy into ablation, adjuvant therapy and therapy. Furthermore, this change in terminology which we strongly support much more clearly delineates the role of ^{131}I in the care of patients with DTC in other disciplines, especially medical oncology. Considering all the factors that have to be weighed in formulating recommendations this is a huge dedicated effort that has come to fruition.

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EDITORIAL

The 2015 Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma: the "evidence-based" refusal to endorse them by EANM due to the "not evidence-based" marginalization of the role of Nuclear Medicine

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In 2007, the American Thyroid Association (ATA) assembled a group of expert clinicians and basic scientists to evaluate published papers and to develop evidence-based guidelines for the diagnosis and management of patients with medullary thyroid carcinoma (MTC). The first ATA guidelines on the management of patients with MTC were published in 2009 [1]. In 2015, ATA released the first revised version of these guidelines [2], in order to assist clinicians of all specialties in the management of these patients.

The ATA Board of Directors selected the Task Force members for elaborating these revised guidelines based on published scientific data in the management of MTC, and included international scientists from the fields of endocrinology, ethics, genetics, medical oncology, molecular biology, nuclear medicine, pathology, paediatrics, radiation oncology, and surgery [2]. Task Force members reviewed relevant articles on MTC by searching MEDLINE/PubMed from January 1980 to April 2014 using specific MTC-related search terms. Task Force members also provided additional relevant articles, book chapters, and other materials. Recommendations were graded using criteria adapted from the United States Preventive Services Task Force Agency for Healthcare Research and Quality as were used in the previous MTC guidelines [1, 2]. After revisions and critical reviews of a series of drafts, the Task Force developed a final document, and the ATA Board of Directors approved the revised set of guidelines [2].

Compared to the earlier version [1], the 2015 revised ATA guidelines on the management of patients with MTC (now consisting of 67 recommendations and related explanatory

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Incidences of Unfavorable Events in the Management of Low-Risk Papillary Microcarcinoma of the Thyroid by Active Surveillance Versus Immediate Surgery

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Background: The incidence of papillary microcarcinoma (PMC) of the thyroid is rapidly increasing globally, making the management of PMC an important clinical issue. Excellent oncological outcomes of active surveillance for low-risk PMC have been reported previously. Here, unfavorable events following active surveillance and surgical treatment for PMC were studied.
Methods: From February 2005 to August 2013, 2153 patients were diagnosed with low-risk PMC. Of these, 1179 patients chose active surveillance and 974 patients chose immediate surgery. The oncological outcomes and the incidences of unfavorable events of these groups were analyzed.
Results: In the active surveillance group, 94 patients underwent surgery for various reasons; tumor enlargement and the appearance of novel lymph node metastases were the reasons in 27 (2.3%) and six patients (0.5%), respectively. One of the patients with conversion to surgery had nodal recurrence, and five patients in the immediate surgery group had a recurrence in a cervical node or unresected thyroid lobe. All of these recurrences were successfully treated. None of the patients had distant metastases, and none died of the disease. The immediate surgery group had significantly higher incidences of transient vocal cord paralysis (VCP), transient hypoparathyroidism, and permanent hypoparathyroidism than the active-surveillance group did (4.1% vs. 0.6%, $p < 0.0001$; 16.7% vs. 2.8%, $p < 0.0001$; and 1.6% vs. 0.08%, $p < 0.0001$, respectively). Permanent VCP occurred only in two patients (0.2%) in the immediate surgery group. The proportion of patients on L-thyroxine for supplemental or thyrotropin (TSH)-suppressive purposes was significantly larger in the immediate surgery group than in the active surveillance group (66.1% vs. 20.7%, $p < 0.0001$). The immediate surgery group had significantly higher incidences of postsurgical hematoma and surgical scar in the neck compared with the active surveillance group (0.5% vs. 0%, $p < 0.05$; and 8.0% vs. 100%, $p < 0.0001$, respectively).
Conclusions: The oncological outcomes of the immediate surgery and active surveillance groups were similarly excellent, but the incidences of unfavorable events were definitely higher in the immediate surgery group. Thus, active surveillance is now recommended as the best choice for patients with low-risk PMC.

Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for approximately 90% of all thyroid malignancies. In 2014, Davies and Welch reported a rapid increase in the incidence of thyroid cancer in the United States, with a 2.9-fold increase over the past 35 years (1). The increase was due to the increase in PTCs of only small size. The proportion of tumors ≤1 cm was reported to reach 39% of all PTCs, whereas the incidences of other types of thyroid cancer have remained stable. A PTC ≤1 cm in maximum diameter is called a papillary microcarcinoma (PMC) of the thyroid (2). Most importantly, the mortality from thyroid cancer has remained stable.

The above data strongly suggest that the increase in the incidence of thyroid cancer is mainly due to the increase in the detection of small PTCs because of the increasing use of many imaging studies. In Korea, the incidence of thyroid cancer attained a 15-fold increase (3), and this increase was also due to an increase in small PTCs; the thyroid cancer

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Papillary thyroid microcarcinoma: time to shift from surgery to active surveillance?

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The incidence of differentiated thyroid cancer is increasing greatly in high-income countries. Roughly 50% of this increase is attributable to the identification of intrathyroidal papillary thyroid microcarcinomas. Since mortality associated with these tumours remains low and stable, the increasing diagnosis has led to concerns about overdiagnosis and overtreatment. Management of papillary thyroid microcarcinomas should take into account the reported absence of mortality when diagnosed in the absence of lymph node metastases and distant metastases, as shown even in recent studies promoting active surveillance; a low recurrence rate of 1–5%; and the risk of permanent complications from surgery that cannot be decreased to less than 1–3%, even in high-volume tertiary care centres with experienced surgeons. On the basis of these data, active surveillance with curative intent, in which active treatment is delayed until the cancer shows signs of significant progression to avoid side-effects of treatment, should be considered in properly selected patients.

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Introduction

Papillary thyroid microcarcinomas are small thyroid cancers measuring 1 cm or less. Most of these tumours are not palpable and are identified either through pathology examination of thyroid glands removed for benign conditions or from imaging procedures such as neck ultrasonography or CT scan for another cause. Much less commonly, papillary thyroid microcarcinoma presents with palpable neck node metastases or distant metastases, leading to the diagnosis of a yet unknown papillary thyroid cancer.

Epidemiology

Occult papillary thyroid microcarcinomas at autopsy

Findings from autopsy studies have shown that occult papillary thyroid microcarcinomas are present in 5–36% of the population (table 1).[1–11] In a meta-analysis of 989 autopsies from 15 studies, the prevalence was 11·5%.[12] Occult papillary thyroid microcarcinomas are characterised by a very small size, with the tumour smaller than 1 mm in 33–79% of cases, and a high frequency of multifocality, which is present in 27–50% of cases (table 1). The prevalence of occult papillary thyroid microcarcinomas is higher in people older than 40 years than in younger people, but is not associated with either iodine intake or sex. The main factor affecting the prevalence of these tumours is the method used for the autopsy analysis.[9] Occult papillary thyroid microcarcinomas represent a major reservoir of unknown thyroid malignancies, which we estimate to affect roughly 20 million adults in the USA and 48 million in Europe. Indeed, the prevalence of occult papillary thyroid microcarcinomas identified at autopsy is 100–1000 times higher than that of clinical cancer.

Clinical papillary thyroid microcarcinomas

There has been a substantial rise in the incidence of thyroid cancer in developed countries during the past 30 years.[13–16] Roughly 50% of this increase is attributable to the identification of intrathyroidal papillary thyroid microcarcinomas, which are present in at least 10% of thyroid glands removed for benign thyroid diseases.[15,17] The most common presentation of thyroid cancer is a papillary thyroid microcarcinoma, measuring less than 2 mm in 60% of patients, in a patient older than 45 years.[18,19] At the same time, mortality from papillary thyroid carcinoma remains low and stable.[17]

Several changes in medical practice in high-income countries have resulted in the increased identification of papillary thyroid microcarcinomas that were previously part of a large subclinical thyroid cancer reservoir. One of these developments is the increased detection of asymptomatic incidental thyroid nodules through highly sensitive imaging procedures, such as the widespread availability of neck ultrasonography that is often used for various neck conditions such as pain, discomfort, or any kind of thyroid disease, and the availability of other imaging procedures that are done for unrelated reasons, such as carotid artery doppler studies, neck MRI for cervical discopathy, and CT scan or ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET scans for non-thyroidal malignancies. Other developments that have led to increased identification of papillary thyroid microcarcinomas are the increased spatial resolution of the latest neck ultrasound machines, which can now detect nodules as small as 2 mm; the increased ability to take biopsy samples from very small thyroid nodules by use of ultrasound-guided fine needle aspiration; and a more thorough histological scrutiny of thyroid specimens obtained at surgery for benign thyroid diseases by sectioning and examining the entire thyroid gland.[20] During the past three decades, a large proportion of thyroid cancer diagnoses—up to 60% according to results from a recent study[21]—can be accounted for by these diagnostic changes. The introduction of a formal screening programme with ultrasonography in South Korea resulted in an increase in diagnosis of thyroid cancer by 15 times within 10 years, with clear concern regarding its usefulness.[22,23] A screening programme initiated in Fukushima following the Daiichi nuclear

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Frequency of High-Risk Characteristics Requiring Total Thyroidectomy for 1–4 cm Well-Differentiated Thyroid Cancer

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Background: The extent of thyroidectomy for low-risk well-differentiated thyroid cancer (WDTC) remains controversial. Historically, total thyroidectomy (TT) has been recommended for WDTC ≥1 cm in size. However, recent National Comprehensive Cancer Network and American Thyroid Association guidelines recognize unilateral thyroid lobectomy as a viable alternative for 1–4 cm cancers due to their otherwise favorable prognosis, with TT remaining the preferred option for tumors with unfavorable pathological characteristics. This study sought to determine how often a completion TT would be recommended based on these guidelines if lobectomy was initially performed in patients with 1–4 cm WDTC without preoperatively known risk factors.
Methods: Patients who underwent thyroidectomy for 1–4 cm WDTC (January 2000 to January 2010) were retrospectively reviewed. Patients with preoperatively known high-risk characteristics, including gross extrathyroidal extension (ETE) on preoperative imaging, clinically apparent lymph node metastases, distant metastases, history of radiation, and positive family history, were excluded. The pathology specimens from the cancer-containing lobe were evaluated for features that would lead to a recommendation for TT based on current guidelines, including aggressive histology, vascular invasion, microscopic ETE, positive margins, and any positive lymph nodes within the specimen.
Results: Of 1000 consecutive patients operated for WDTC, 287 would have been eligible for lobectomy as the initial operation. The mean age in this cohort was 45 years, and 80% were women. Aggressive tall-cell variant histology was found in one patient (0.5%), angio-invasion in 34 (12%), ETE in 48 (17%), positive margins in 51 (18%), and positive lymph nodes in 49 (18%) patients. Completion TT would have been recommended in 122/287 (43%) patients. Even in those with 1–2 cm cancers, completion TT would have been recommended in 52/143 (36%) patients.
Conclusions: Nearly half of the patients with 1–4 cm WDTC who are eligible for lobectomy under current guidelines would require completion TT based on pathological characteristics of the initial lobe. Surgeons, endocrinologists, and patients need to balance the relative benefits, risks, and costs of initial TT versus the possible need for reoperative completion TT.

Introduction

The extent of thyroidectomy for low-risk well-differentiated thyroid cancer (WDTC) remains an area of controversy. Total thyroidectomy (TT) has traditionally been recommended for thyroid cancers >1 cm (1,2). Several recent publications, however, have suggested that the extent of thyroidectomy—specifically, TT versus unilateral thyroid lobectomy—may not lead to significant differences in long-term outcomes for patients with WDTC up to 4 cm in size, likely because of the indolent nature of the majority of these tumors (3,4). Based on these data, recent guidelines for the management of WDTC have proposed thyroid lobectomy as an adequate surgical treatment for WDTC 1–4 cm in size in the absence of certain high-risk characteristics (5,6). Some of these characteristics can be determined before or during thyroidectomy, and include evidence of gross extrathyroidal extension (ETE), locoregional or distant metastases, and a

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LETTERS TO THE EDITOR

Apparently intrathyroid papillary thyroid carcinoma >1 and ≤4 cm: is the need for completion thyroidectomy common among patients submitted to lobectomy?

Dear Editor,

Many authors recommend total thyroidectomy for patients with papillary thyroid carcinoma (PTC) >1 cm, even if the tumour is sporadic, unilateral, ≤4 cm and apparently restricted to the thyroid.[1] In the last edition of the guidelines of the British Thyroid Association (BTA), lobectomy is as accepted for the treatment of patients with PTC as total thyroidectomy if nodular disease is unilateral and the tumour is sporadic, measures ≤4 cm and exhibits no extrathyroid extension (ETE) or apparent lymph node (LN) metastases (cN0).[2] However, some patients submitted to lobectomy may be classified as intermediate risk after surgery based on the histological findings. Total thyroidectomy would be more indicated for these patients, who are frequently also candidates for adjuvant therapy with ^{131}I.[1,2]

We evaluated the percentage of patients who would be treated by lobectomy according to BTA, but in whom histology reveals findings that change the initial classification from low to intermediate risk and for whom total thyroidectomy and even therapy with ^{131}I would be most appropriate.[1,2]

Patients seen at our institution with thyroid nodules >1 and ≤4 cm and cytology of PTC were initially selected. Excluded were patients with (i) familial PTC; (ii) a history of neck radiotherapy; pre-operative ultrasonography (US) showing (iii) bilateral nodular disease, (iv) ETE of the tumour, or (v) suspicious cervical LN.[2–4] Patients exhibiting nodules with benign cytology or nodules ≤1 cm with nonsuspicious US findings ipsilateral to PTC were included.

All patients were submitted to total thyroidectomy by surgeons experienced in thyroid surgery. Lymph node dissection was performed only in the case of a suspicion of LN involvement during perioperative assessment (inspection and palpation by the surgeon during thyroidectomy).[1,2] Patients with LN involvement or ETE suspected during perioperative assessment were excluded. The recommendation of change from the initial indication of lobectomy to total thyroidectomy during surgery also exists in these cases.

Histological analysis of the thyroid lobe with PTC diagnosed before surgery was performed, and the following findings were considered: vascular invasion, aggressive histological subtype (tall cell, columnar cell, poorly differentiated), ETE and tumour-positive margins. The finding of an additional and microscopic focus of the tumour was not considered relevant.

US was performed with a linear multifrequency 14-MHz transducer for morphological analysis and for power Doppler evaluation. The images were analysed by experienced professionals.

Cytology and histology smears were analysed by pathologists experienced in thyroid pathology.

One hundred eighty patients, 156 women and 24 men, with age raging of 15–80 years (median 43 years), were included. Tumour size ranged from 11 to 40 mm (median 22 mm). Vascular invasion was observed in 14 (7·7%) patients. Only one tumour was of the aggressive histological subtype (tall cell). ETE was observed in 42 patients (23·3%). Tumour resection was microscopically incomplete (positive margins) in 12 patients (6·6%). Thus, 54 (30%) initially low-risk patients (T1-2cN0) were finally classified as intermediate risk.[2] According to BTA[2] and European Society for Medical Oncology[1], these patients would also be candidates for therapy with ^{131}I (incomplete tumour resection or tumour >1 cm with aggressive histology and/or ETE). Of note, additional and microscopic tumour foci (the largest measuring 4 mm) were detected in 28 patients (15·5%), which were contralateral to the known tumour in 14 (7·7%).

Our results show that 30% of patients with PTC >1 and ≤4 cm, who are initially classified as low risk based on pre- and perioperative evaluations, are reclassified after surgery as intermediate risk based on the histological findings (of the thyroid lobe with known tumour). This rate is higher if elective central compartment LN dissection is performed, as LN involvement is frequent in cN0 patients.[5] However, this procedure is not recommended for patients with apparently T1-2cN0 tumours.[1,2] We emphasize that this risk of 30% considers that all intermediate-risk patients will require surgical completion. However, this procedure, followed or not by adjuvant therapy with ^{131}I, may not be necessary in all patients with ETE, especially when tumour resection was complete.

We conclude that the possibility for surgical completion does not appear to be so frequent in order to weaken lobectomy as a treatment option in patients with sporadic and unilateral PTC >1 and ≤4 cm, in the absence of a suspicion of ETE or LN involvement during pre- and perioperative assessment. However, individually, the patient may consider a risk of reoperation of 30% to be high, or even that this risk (of a new surgery) would only compensate if complications would be much more frequent with total thyroidectomy.[6] These possibilities should be considered in the decision-making process.

Disclosure statement

The authors declare that no competing financial interests exist.

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A Prospective Study Showing an Excellent Response of Patients with Low-Risk Differentiated Thyroid Cancer Who Did Not Undergo Radioiodine Remnant Ablation after Total Thyroidectomy

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Key Words
Low-risk thyroid carcinoma · Thyroglobulin · Thyroglobulin temporal trend · Radioiodine remnant ablation · Neck ultrasound

Abstract
Objectives: To prospectively evaluate the outcome of patients with low-risk papillary thyroid carcinoma treated with total thyroidectomy (TT) who did not undergo radioiodine remnant ablation (RRA). ***Study Design:*** We prospectively followed up 57 patients; 3 months after TT, thyroglobulin (Tg) assessment and neck ultrasonography (US) were performed while patients were taking L-T_4, presenting suppressed TSH. Six months after TT, patients underwent stimulated Tg testing and whole-body scan (WBS) after recombinant TSH (rhTSH). Then, 18 months after TT, the patients were evaluated by neck US and Tg under TSH between 0.5 and 2.0 mIU/ml. Two years after TT, we performed another rhTSH assessment, measuring Tg and making a WBS. The patients were then annually monitored with neck US and Tg measurement under TSH between 0.5 and 2.0 mIU/l for 36–84 months. ***Results:*** Neck US of all patients, 3 months after TT, presented no evidence of abnormal residual tissues or metastatic lymph nodes (negative neck US); at this time, the mean Tg level was 0.42 ng/ml. Six months after surgery, after rhTSH, the mean thyroid bed uptake was 1.82%, and Tg levels ranged from 0.10 to 22.30 ng/ml (mean, 2.89 ng/ml). The patients were followed up without any sign of recurrence (negative neck US and stable or decreasing Tg levels). During the ongoing follow-up, the Tg trend was stable or decreasing, independently of the initial suppressed or stimulated Tg level, or WBS uptake. ***Conclusions:*** In patients with low-risk differentiated thyroid cancer, who were operated by TT and who did not undergo RRA, an excellent response to treatment may be confirmed by annual neck US and Tg trend.

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Dynamic Risk Stratification in Patients with Differentiated Thyroid Cancer Treated Without Radioactive Iodine

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Context: Although response to therapy assessment is a validated tool for dynamic risk stratification in patients with differentiated thyroid cancer (DTC) treated with total thyroidectomy (TT) and radioactive iodine therapy (RAI), it has not been well studied in patients treated with lobectomy or TT without RAI. Because these responses to therapy definitions are heavily dependent on serum thyroglobulin (Tg) levels, modifications of the original definitions were needed to appropriately classify patients treated without RAI.

Objective: This study aimed to validate the response to therapy assessment in patients with DTC treated with lobectomy or TT without RAI.

Design and Setting: This was a retrospective study, which took place at a referral center.

Patients: A total of 507 adults with DTC were treated with lobectomy (n = 187) or TT (n = 320) without RAI. They had a median age of 43.7 y, 88% were female, 85.4% had low risk, and 14.6% intermediate risk.

Main Outcome Measure: Main outcome measured was recurrent/persistent structural evidence of disease (SED) during a median followup period of 100.5 months (24–510).

Results: Recurrent/persistent SED was observed in 0% of the patients with excellent response to therapy (nonstimulated Tg for TT $<$ 0.2 ng/mL and for lobectomy $<$ 30 ng/mL, undetectable Tg antibodies [TgAb] and negative imaging; n = 326); 1.3% with indeterminate response (nonstimulated Tg for TT 0.2–5 ng/mL, stable or declining TgAb and/or nonspecific imaging findings; n = 2/152); 31.6% of the patients with biochemical incomplete response (nonstimulated Tg for TT $>$ 5 ng/mL and for lobectomy $>$ 30 ng/mL and/or increasing Tg with similar TSH levels and/or increasing TgAb and negative imaging; n = 6/19) and all (100%) patients with structural incomplete response (n = 10/10) ($P < .0001$). Initial American Thyroid Association risk estimates were significantly modified based on response to therapy assessment.

Conclusions: Our data validate the newly proposed response to therapy assessment in patients with DTC treated with lobectomy or TT without RAI as an effective tool to modify initial risk estimates of recurrent/persistent SED and better tailor followup and future therapeutic approaches. This study provides further evidence to support a selective use of RAI in DTC. **(*J Clin Endocrinol Metab* 101: 2692–2700, 2016)**

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Abbreviations: AJCC/UICC, American Joint Cancer Committee/Union Internationale Contre le Cancer; ATA, American Thyroid Association; DTC, differentiated thyroid cancer; MSKCC, Memorial Sloan Kettering Cancer Center; RAI, radioactive iodine therapy; SED, structural evidence of disease; Tg, thyroglobulin; TgAb, antithyroglobulin antibody; TT, thyroidectomy; US, ultrasound.

Genetic variants associated with antithyroid drug-induced agranulocytosis: a genome-wide association study in a European population

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Summary

Background **Drug-induced agranulocytosis is a potentially life-threatening adverse reaction. Genome-wide association studies (GWASs) in ethnic Chinese people in Taiwan and Hong Kong have shown an association between agranulocytosis induced by antithyroid drugs and the HLA alleles *HLA-B*38:02* and *HLA-DRB1*08:03*. We aimed to identify genetic variants associated with antithyroid drug-induced agranulocytosis in a white European population.**

Methods **We did a GWAS in 234 European adults with any non-chemotherapy drug-induced agranulocytosis (absolute neutrophil count ≤0·5×10⁹/L [≤500/μL]) and 5170 population controls. 39 of the 234 patients had agranulocytosis that was induced by antithyroid drugs (thiamazole [methimazole], carbimazole, or propylthiouracil). After imputation and HLA allele prediction, 9 380 034 single nucleotide polymorphisms (SNPs) and 180 HLA alleles were tested for association. The genome-wide significance threshold was $p<5\times10^{-8}$.**

Findings **Agranulocytosis induced by non-chemotherapy drugs in general was significantly associated with the HLA region on chromosome 6, with odds ratios (ORs) of 3·24 (95% CI 2·31–4·55, $p=1\cdot20\times10^{-11}$) for *HLA-B*27:05* and 3·57 (2·61–4·90, $p=2\cdot32\times10^{-15}$) for the top SNP (rs114291795). Drug-specific analysis showed that the association with *HLA-B*27:05* was largely driven by cases induced by antithyroid drugs. In a multiple logistic regression model, the OR for *HLA-B*27:05* was 7·30 (3·81–13·96) when antithyroid drug-induced agranulocytosis was compared with population controls ($p=1\cdot91\times10^{-9}$) and 16·91 (3·44–83·17) when compared with a small group of hyperthyroid controls ($p=5\cdot04\times10^{-4}$). Three SNPs were strongly associated with antithyroid drug-induced agranulocytosis: rs652888 (OR 4·73, 95% CI 3·00–7·44, $p=1\cdot92\times10^{-11}$) and rs199564443 (17·42, 7·38–41·12, $p=7\cdot04\times10^{-11}$), which were independent of *HLA-B*27:05*, and rs1071816 (5·27, 3·06–9·10, $p=2\cdot35\times10^{-9}$) which was in moderate linkage disequilibrium with *HLA-B*27:05*. In heterozygous carriers of all three SNPs, the predicted probability of antithyroid drug-induced agranulocytosis was about 30% (OR 753, 95% CI 105–6812). To avoid one case of agranulocytosis, based on the possible risk reduction if all three SNPs are genotyped and carriers are treated or monitored differently from non-carriers, roughly 238 patients would need to be genotyped.**

Interpretation **In white European people, antithyroid drug-induced agranulocytosis was associated with *HLA-B*27:05* and with other SNPs on chromosome 6. In the future, carriers of these variants could be placed under intensified monitoring or offered alternative treatment for hyperthyroidism.**

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Introduction

Serious adverse drug reactions such as drug-induced agranulocytosis can severely limit the use of a drug. Agranulocytosis is defined as a decline in absolute neutrophil count to less than 0·5×10⁹/L (<500/μL).[1] It is causally related to more than 125 non-chemotherapy drugs, and among the most well documented are the thiourea drugs thiamazole (methimazole), carbimazole, and propylthiouracil, which are used for the treatment of hyperthyroidism.[2,3] The risk of agranulocytosis induced by antithyroid drugs is estimated to be 0·2–0·5%, and onset is typically in the first 3 months of treatment.[3,4] Patients often present with symptoms of infection, such as fever, chills, and myalgias.[5] Left untreated, sepsis will develop in roughly two-thirds of patients.[6] Even with appropriate management, the mortality rate for agranulocytosis induced by non-chemotherapy drugs is 4–5%.[6]

The pathogenic mechanism behind drug-induced agranulocytosis is not well established. Antibodies against circulating neutrophils have been identified in patients, which suggests an immunological mechanism.[7] Another postulated mechanism is induction of T-cell-mediated reactions against neutrophils and neutrophil precursors in the bone marrow by oxidative drug metabolites.[7]

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Synthetic gene network restoring endogenous pituitary–thyroid feedback control in experimental Graves' disease

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Graves' disease is an autoimmune disorder that causes hyperthyroidism because of autoantibodies that bind to the thyroid-stimulating hormone receptor (TSHR) on the thyroid gland, triggering thyroid hormone release. The physiological control of thyroid hormone homeostasis by the feedback loops involving the hypothalamus–pituitary–thyroid axis is disrupted by these stimulating autoantibodies. To reset the endogenous thyrotrophic feedback control, we designed a synthetic mammalian gene circuit that maintains thyroid hormone homeostasis by monitoring thyroid hormone levels and coordinating the expression of a thyroid-stimulating hormone receptor antagonist (TSH_{Antag}), which competitively inhibits the binding of thyroid-stimulating hormone or the human autoantibody to TSHR. This synthetic control device consists of a synthetic thyroid-sensing receptor (TSR), a yeast Gal4 protein/human thyroid receptor-α fusion, which reversibly triggers expression of the TSH_{Antag} gene from TSR-dependent promoters. In hyperthyroid mice, this synthetic circuit sensed pathological thyroid hormone levels and restored the thyrotrophic feedback control of the hypothalamus–pituitary–thyroid axis to euthyroid hormone levels. Therapeutic plug and play gene circuits that restore physiological feedback control in metabolic disorders foster advanced gene- and cell-based therapies.

synthetic biology | cell engineering | designer cells | gene switch | prosthetic networks

Thyroid hormones impact the function of all tissues and affect essentially every major pathway, including thermogenesis, carbohydrate metabolism, and lipid homeostasis (1). The thyroid gland releases a mixture of the thyroid hormones triiodothyronine (T3; 20%) and thyroxine (T4; 80%), which is converted to the more potent agonist T3 by type II deiodinase (DIO2) in the CNS (hypothalamus and the pituitary gland) or DIO1/2 in the peripheral tissues (e.g., liver, muscle, and heart) (2, 3). DIO1 and DIO2 sensitize target cells to T4 by triggering its deiodination to the more potent hormone T3 (3). The thyroid hormones, particularly T3, exert their action by nuclear thyroid hormone receptors, TRα and TRβ, which are differentially expressed in tissues and have distinct roles in thyroid hormone control of various target genes, such as *uncoupling protein 1*, *HMG-CoA reductase*, and *phosphoenolpyruvate carboxy kinase* (1). The TRα and TRβ can activate or repress gene expression depending on the target–promoter context in the target cells (4). The concentration of thyroid hormones in the body is tightly regulated by the combination of classical activation loops initiated at low thyroid hormone levels and negative feedback loops initiated by high thyroid hormone levels operating along the hypothalamus–pituitary–thyroid axis (2, 3) (Fig. 1*A*). At low thyroid hormone (T3 and T4) levels, the hypothalamus releases the thyroid-stimulating hormone (TSH) -releasing hormone, which binds and activates the TSH-releasing hormone receptor to stimulate the release of the TSH by the pituitary gland (activation loop) (5). TSH binding to the thyroid-stimulating hormone receptor (TSHR) in the thyroid gland stimulates the production and release of the T3/T4 mixture, which completes the activation loops along the hypothalamus–pituitary–thyroid axis (2, 3). To maintain the thyroid hormones at a homeostasis level and prevent hyperthyroidism by ill-controlled activation of the hypothalamus–pituitary–thyroid axis, the circulating thyroid hormones trigger a negative feedback loop by binding to the TRs in the hypothalamus and the pituitary gland and repress TSH-releasing hormone and TSH release, respectively (6) (Fig. 1*A*).

In humans, hyperthyroidism is mostly the result of an overactive thyroid gland caused by thyroid-stimulating autoantibodies (Graves' disease) or autonomous TSH-secreting pituitary and thyroid hormone-secreting thyroid adenomas, resulting in elevated blood thyroid hormone levels (7). Hyperthyroid symptoms include nervousness, increased sweating, weight loss, tachycardia, palpitations, hyperactivity, and tremor and are associated with serious complications, including life-threatening cardiac arrhythmia or psychosis if left untreated (8). Graves' disease, the most common cause of hyperthyroidism, is an autoimmune disorder characterized by the production of thyroid-stimulating hormone receptor-stimulating antibodies (TSAbs) that trigger constitutive thyroid hormone production and release from the thyroid gland (9–11). The TSHR is also expressed in ocular connective tissue and represents a candidate autoantigen for development of Graves' orbitopathy, an ocular manifestation of the disease that, in rare cases, may result in sight-impeding expansion of orbital tissue with inflammation,

Significance

Graves' disease is caused by autoantibodies that activate the thyroid-stimulating hormone (TSH) receptor and trigger a chronic increase in thyroid hormone levels. Current treatment options remain unchanged for decades and include antithyroid drugs as well as radioiodine treatment and thyroidectomy, which result in the destruction of the thyroid gland and require lifelong prescription of thyroid hormones. We designed a closed-loop gene circuit that enables engineered cells to monitor increased thyroid hormone levels and drive the expression of a validated TSH receptor antagonist that competes with TSH as well as TSH receptor autoantibodies, thereby overcoming the pathophysiological activation of the thyroid gland. Hyperthyroid animals implanted with these designer cells had thyroid hormone levels corrected by restoring the feedback control system of the hypothalamus–pituitary–thyroid axis.

Author contributions: P.S., G.C.-E.H., M. Folcher, H.Z., and M. Fussenegger designed research; P.S. and G.C.-E.H. performed research; P.S., M. Folcher, H.Z., and M. Fussenegger analyzed data; and P.S., M. Folcher, H.Z., and M. Fussenegger wrote the paper.

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Antithyroid Drug Side Effects in the Population and in Pregnancy

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Objective: Methimazole (MMI) and propylthiouracil (PTU) are both associated with birth defects and may also rarely be associated with agranulocytosis and liver failure. The frequency of these side effects when antithyroid drugs (ATDs) are used in the population in general or in pregnancy remains to be elucidated.

Design: All individuals registered as the parent of a live-born child in Denmark, 1973–2008, were identified (n = 2 299 952) and studied from 1995 through 2010 for the use of ATDs. Outcomes were agranulocytosis, liver failure, and birth defects in their offspring. To evaluate the frequency of these side effects associated with the use of ATDs in pregnancy, all live-born pregnancies (n = 830 680), 1996–2008, were identified in a subanalysis.

Results: In the population studied, 28 998 individuals redeemed prescriptions of ATDs (exposure in 2115 pregnancies), which was associated with 45 cases of agranulocytosis (one in pregnancy) and 10 cases of liver failure (one in pregnancy). This corresponded to 41 and 11 cases of agranulocytosis and liver failure per 5 million inhabitants during a 10-year period (agranulocytosis: 0.16% of ATDs exposed [MMI: 0.11% vs PTU: 0.27%, $P = .02$]; liver failure: 0.03% of ATDs exposed [MMI: 0.03% vs PTU: 0.05%, $P = .4$]). The majority (83%) developed the side effect within 3 months of ATD treatment and 25% during hyperthyroidism relapse. The use of ATDs in pregnancy was associated with birth defects in 3.4% of exposed children (44 cases per 5 million inhabitants per 10 y), and the frequency of birth defects after ATD exposure was 75 times higher than both maternal agranulocytosis and liver failure in pregnancy.

Conclusions: In the Danish population in general, ATDs associated birth defects and agranulocytosis had similar frequencies and were more common than liver failure, whereas for the use of ATDs in pregnancy, birth defects were dominant. The burden of side effects to the use of ATDs can be reduced by restricting the use of ATDs in early pregnancy. (***J Clin Endocrinol Metab*** **101: 1606–1614, 2016)**

Untreated or inadequately treated hyperthyroidism in pregnancy may adversely impact the health of the pregnant woman and the development of the fetus (1). Thus, treatment of hyperthyroidism in pregnant women is imperative, but the use of antithyroid drugs (ATDs) in the teratogenic period of early pregnancy is associated with an increased prevalence of birth defects (2). Birth defects may be severe and may considerably influence the life of the child and the family. Consequently, the risk and type of birth defects associated with the use of methimazole (MMI)/carbimazole (CMZ) and propylthiouracil (PTU) are important to consider in clinical guidance on the management of maternal hyperthyroidism in pregnancy (3–5). The MMI/CMZ embryopathy including severe birth defects has been described for decades (6), whereas the finding that the use of PTU in early pregnancy also was asso-

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Abbreviations: ATD, antithyroid drug; CMZ, carbimazole; ICD, *International Classification of Disease*; MBR, Medical Birth Register; MMI, methimazole; PTU, propylthiouracil.

Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study

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Summary

Background Thyroid hormone is involved in the regulation of early brain development. Since the fetal thyroid gland is not fully functional until week 18–20 of pregnancy, neuronal migration and other crucial early stages of intrauterine brain development largely depend on the supply of maternal thyroid hormone. Current clinical practice mostly focuses on preventing the negative consequences of low thyroid hormone concentrations, but data from animal studies have shown that both low and high concentrations of thyroid hormone have negative effects on offspring brain development. We aimed to investigate the association of maternal thyroid function with child intelligence quotient (IQ) and brain morphology.

Methods In this population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands), we investigated the association of maternal thyroid function with child IQ (assessed by non-verbal intelligence tests) and brain morphology (assessed on brain MRI scans). Eligible women were those living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. For this study, women with available serum samples who presented in early pregnancy (<18 weeks) were included. Data for maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at weeks 9–18 of pregnancy), and child IQ (assessed at a median of 6·0 years of age [95% range 5·6–7·9 years]) or brain MRI scans (done at a median of 8·0 years of age [6·2–10·0]) were obtained. Analyses were adjusted for potential confounders including concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free thyroxine.

Findings Data for child IQ were available for 3839 mother–child pairs, and MRI scans were available from 646 children. Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (p=0·0044), child grey matter volume (p=0·0062), and cortex volume (p=0·0011). For both low and high maternal free thyroxine concentrations, this association corresponded to a 1·4–3·8 points reduction in mean child IQ. Maternal thyroid-stimulating hormone was not associated with child IQ or brain morphology. All associations remained similar after the exclusion of women with overt hypothyroidism and overt hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or positivity).

Interpretation Both low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume. The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results.

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See Comment page 3

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Introduction

Mild maternal thyroid hormone deficiency occurs in about 5–18% of all pregnant women worldwide, depending on the definition used.[1–4] Thyroid hormone is crucial for intrauterine neurodevelopment because it regulates migration, proliferation, and differentiation of fetal neuronal cells that form grey matter later in life, as well as synaptogenesis and myelination.[5,6] In human beings, early neurogenesis starts from approximately 5 weeks post conception and thyroid hormone receptors have been detected in fetal brain from as early as 8 weeks.[7] Since the fetal thyroid gland is not functionally matured before week 18–20 of pregnancy,[8] the fetus largely depends on the supply of maternal thyroxine during the early stages of intrauterine brain development.

Results from animal studies have shown that shortage of thyroid hormone impairs brain development and affects brain morphology.[5,6] Brain morphology, particularly relative grey matter volume and cortical thickness, shows a consistent positive association with intelligence quotient (IQ).[9] Data from population studies have shown that the offspring of women with low free

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ORIGINAL ARTICLE

Maternal total T4 during the first half of pregnancy: physiologic aspects and the risk of adverse outcomes in comparison with free T4

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Summary

Aim We aimed to investigate TT4 physiological aspects and associations with clinical end-points.

Background Total T4 (TT4) has been suggested as a marker for maternal thyroid function during pregnancy because as compared to FT4 (i) TT4 measurement is not affected by binding protein interference, (ii) TT4 is considered to be more stable from the second trimester onwards, and (iii) TT4 better reflects changes in the hypothalamic–pituitary–thyroid axis. However, this is based on data from small studies, and, more importantly, it is unknown whether TT4 is associated with adverse pregnancy or child outcomes.

Methods We selected 5647 mother–child pairs from a large population-based prospective cohort with data on maternal TSH, FT4 and TT4 during early pregnancy (median 13·2 weeks, 95% range 9·8–17·6). We used multivariable (non)linear and logistic regression models to study the association of maternal TT4 with pre-eclampsia, premature delivery, birthweight and offspring IQ and compare the results with previously obtained results for FT4.

Results The change of mean TT4 levels was 27·5% compared to 20·2% for FT4. There was a log-linear association of TT4 and FT4 with TSH, but the explained variability of TSH was much lower for TT4 than for FT4 (R-squared TT4: 2·5% *vs* 8·0% for FT4). In contrast to FT4, there was no independent association of maternal TT4 with pre-eclampsia, premature delivery, birthweight or offspring IQ.

Conclusion Maternal TT4 levels are highly variable in the first half of pregnancy and are poorly related to maternal TSH. This study shows that maternal TT4 levels are either not associated, or not better associated as compared to FT4, with adverse pregnancy or child outcomes. This suggests that the maternal TT4 is inferior to FT4 in the assessment of maternal thyroid function during the first half of pregnancy.

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Introduction

Adequate thyroid hormone availability during early pregnancy is essential for a normal pregnancy outcome as well as proper foetal growth and development. Gestational thyroid dysfunction has been associated with an increased risk of adverse clinical outcomes, including pre-eclampsia, premature delivery, adverse effects on birthweight and cognitive development of the child.[1–4] The majority of physicians use both TSH and FT4 for the assessment of maternal thyroid function during pregnancy.[5–8] However, several immunoassays may not adequately measure FT4 levels due to the high protein binding state that is present during pregnancy, particularly during late pregnancy.[9] This is one of the main reasons that current guidelines of the American Thyroid Association (ATA), the Endocrine Society (ES) and the European Thyroid Association (ETA) suggest TT4 as an alternative measure for maternal thyroid function during pregnancy.[10–12]

Apart from the fact that TT4 assays are less affected by differences in binding proteins, various other (physiological) arguments may favour the use of TT4 over FT4. First of all, TT4 levels are reported to be more stable throughout pregnancy compared to FT4 levels.[9–11] Secondly, TT4 levels may have a better log-linear relationship with maternal TSH than FT4, thus

Maternal hypothyroxinaemia in pregnancy is associated with obesity and adverse maternal metabolic parameters

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Abstract

Objective: Subclinical hypothyroidism and isolated hypothyroxinaemia in pregnancy have been associated with an increased risk of gestational diabetes. We aimed to ascertain if these women have a worse metabolic phenotype than euthyroid pregnant women.

Design, subjects and methods: We recruited 956 healthy Caucasian women with singleton, non-diabetic pregnancies from routine antenatal clinics. Detailed anthropometric measurements (including BMI and skinfold thickness) and fasting blood samples (for TSH, free thyroxine (FT_4), free triiodothyronine (FT_3), HbA1c, lipid profile, plasma glucose and insulin resistance (HOMA-IR) analysis) were obtained at 28 weeks gestation.

Results: In comparison to euthyroid women ($n=741$), women with isolated hypothyroxinaemia ($n=82$) had significantly increased BMI (29.5 vs 27.5 kg/m^2, $P<0.001$), sum of skinfolds (57.5 vs 51.3 mm, $P=0.002$), fasting plasma glucose (4.5 vs 4.3 mmol/l, $P=0.01$), triglycerides (2.3 vs 2.0 mmol/l, $P<0.001$) and HOMA-IR (2.0 vs 1.3, $P=0.001$). Metabolic parameters in women with subclinical hypothyroidism ($n=133$) were similar to those in euthyroid women. Maternal FT_4 was negatively associated with BMI ($r=-0.22$), HbA1c ($r=-0.14$), triglycerides ($r=-0.17$), HOMA-IR ($r=-0.15$) but not total/HDL cholesterol ratio ($r=-0.03$). Maternal FT_3:FT_4 ratio was positively associated with BMI ($r=0.4$), HbA1c ($r=0.21$), triglycerides ($r=0.2$), HOMA–IR ($r=0.33$) and total/HDL cholesterol ratio ($r=0.07$). TSH was not associated with the metabolic parameters assessed.

Conclusions: Isolated hypothyroxinaemia, but not subclinical hypothyroidism, is associated with adverse metabolic phenotype in pregnancy, as is decreasing maternal FT_4 and increasing FT_3:FT_4 ratio. These associations may be a reflection of changes in the thyroid hormone levels secondary to increase in BMI rather than changes in thyroid hormone levels affecting body weight and related metabolic parameters.

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Introduction

Recently, increasing numbers of studies have shown associations between mild maternal thyroid hormone insufficiency (including subclinical hypothyroidism and isolated hypothyroxinaemia) in pregnancy and impaired neuropsychological development of the offspring, as well as several obstetric complications, such as miscarriage, preterm delivery, gestational hypertension and pre-eclampsia (1, 2, 3). Several of these studies (4, 5, 6), although not all (7, 8) have also shown that subclinical hypothyroidism in pregnancy is associated with an increased risk of gestational diabetes. Isolated hypothyroxinaemia has also been shown to be associated with

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Impact of Levothyroxine in Miscarriage and Preterm Delivery Rates in First Trimester Thyroid Antibody-Positive Women With TSH Less Than 2.5 mIU/L

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Background: Thyroid disease during pregnancy is associated with multiple adverse maternal and fetal outcomes. In particular, multiple observational studies have demonstrated an association between the presence of thyroid antibodies in euthyroid women in the first trimester of miscarriage and an increased rate of spontaneous miscarriage and preterm delivery. The present study is a prospective intervention trial of the effect of levothyroxine on the rate of miscarriage and preterm delivery in euthyroid thyroid-antibody positive women in the first trimester of pregnancy.

Methods: A total of 8530 women in the first trimester of pregnancy in Southern Italy were screened for TSH and thyroid antibodies. Group A consisted of 198 euthyroid thyroid antibody positive women treated with levothyroxine, group B consisted of 195 untreated euthyroid thyroid antibody positive women, and group C consisted of 197 untreated thyroid antibody negative women.

Results: The rate of miscarriage did not differ between the 3 groups (11.6%, 14.9%, and 8.1 %, $P = .11$). The rate of preterm delivery between the 3 groups was 6.9%, 10.8%, and 2.8% and was statistically significant ($P = .01$). The rate of preterm delivery was significantly different between groups B and C ($P = .02$) but was not significantly different between groups A and B ($P = .27$).

Conclusions: In conclusion, the present study found that levothyroxine intervention had no impact on the rate of miscarriage and preterm delivery in euthyroid thyroid antibody positive women. **(*J Clin Endocrinol Metab* 101: 3685–3690, 2016)**

Thyroid disease during pregnancy is associated with multiple adverse outcomes in the developing fetus, mother, and on the neurocognitive development of the offspring (1). For decades, it has been known that overt thyroid dysfunction, both overt hypothyroidism and overt hyperthyroidism, is linked to pregnancy loss, polyhydramnios, gestational hypertension, preterm delivery, preeclampsia, and decreased intelligence quotient in the offspring (2). Furthermore, treatment of overt thyroid disease has been documented to prevent these complications (3). Accordingly, both Thyroid and Obstetrical Societies advocate treating all women with overt thyroid dysfunction (4–6).

The impact of subclinical thyroid disease on pregnancy, and whether or not to treat, remains controversial. Most studies have shown that subclinical hyperthyroidism has no deleterious impact during pregnancy (7). However, an ever increasing body of literature has documented multiple adverse outcomes of subclinical hypothyroidism in pregnancy including spontaneous pregnancy loss, gestational diabetes mellitus, gestational hypertension, placental abruption, and impaired neurocognitive development in the offspring (8–12). Two intervention trials have been published on the impact of levothyroxine intervention for subclinical hypothyroidism with divergent results. Lazarus et al (13) found no impact on the intelligence

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Abbreviations: CI = confidence interval; RR = relative risk; TPO-Ab+, thyroid peroxidase antibody positive.

Subclinical Hypothyroidism and Thyroid Autoimmunity Are Not Associated With Fecundity, Pregnancy Loss, or Live Birth

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Context: Prior studies examining associations between subclinical hypothyroidism and antithyroid antibodies with early pregnancy loss and live birth suggest mixed results and time to pregnancy (TTP) has not been studied in this patient population.

Objective: This study sought to examine associations of prepregnancy TSH concentrations and thyroid autoimmunity with TTP, pregnancy loss, and live birth among women with proven fecundity and a history of pregnancy loss.

Design and Setting: This was a prospective cohort study from a large, randomized controlled trial that took place at four medical centers in the United States.

Patients or Other Participants: Healthy women, ages 18–40 y, who were actively attempting to conceive and had one or two prior pregnancy losses and no history of infertility were eligible for the study.

Intervention: There were no interventions.

Main Outcome Measure: TTP, pregnancy loss, and live birth.

Results: Women with TSH $\geq$ 2.5 mIU/L did not have an increased risk of pregnancy loss (risk ratio, 1.07; 95% confidence interval [CI], 0.81–1.41) or a decrease in live birth rate (risk ratio, 0.97; 95% CI, 0.88–1.07) or TTP (fecundability odds ratio, 1.09; 95% CI, 0.90–1.31) compared with women with TSH $<$2.5 mIU/L after adjustment for age and body mass index. Similar findings were observed for women with thyroid autoimmunity and after additional adjustment for treatment assignment.

Conclusions: Among healthy fecund women with a history pregnancy loss, TSH levels $\geq$ 2.5 mIU/L or the presence of antithyroid antibodies were not associated with fecundity, pregnancy loss, or live birth. Thus, women with subclinical hypothyroidism or thyroid autoimmunity can be reassured that their chances of conceiving and achieving a live birth are likely unaffected by marginal thyroid dysfunction. **(*J Clin Endocrinol Metab* 101: 2358–2365, 2016)**

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Abbreviations: Anti-TG, thyroid globulin antibody; BMI, body mass index; CI, confidence interval; CV, coefficient of variation; EAGeR, Effects of Aspirin in Gestation and Reproduction; FASTER, First and Second Trimester Evaluation of Risk; FOR, fecundability odds ratio; hCG, human chorionic gonadotropin; LDA, low-dose aspirin; RR, risk ratio; TTP, time to pregnancy.

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Effects of Levothyroxine Therapy on Pregnancy Outcomes in Women with Subclinical Hypothyroidism

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Background: Subclinical hypothyroidism (SCH) has been associated with increased risk of adverse pregnancy outcomes in some, but not all, studies. Uncertainty remains regarding the impact of levothyroxine (LT4) therapy on improving health outcomes in pregnant women with SCH. The objective of this study was to assess the potential benefits of LT4 therapy in pregnant women with SCH.
Methods: The medical records were reviewed of pregnant women with SCH, defined as an elevated serum thyrotropin (TSH) of >2.5 mIU/L for the 1st trimester or >3 mIU/L for the 2nd and 3rd trimesters, but ≤10 mIU/L. Pregnant women were divided into two groups depending on whether they received LT4 (group A) or not (group B). Pregnancy loss and other pre-specified adverse outcomes were evaluated during follow-up.
Results: There were 82 women in group A and 284 in group B. Group A had a higher body mass index ($p = 0.04$) and a higher serum TSH level ($p < 0.0001$) compared with group B. Group A had fewer pregnancies lost ($n = 5$ [6.1%] vs. $n = 25$ [8.8%]; $p = 0.12$), low birth weight (LBW) offspring (1.3% vs. 10%; $p < 0.001$), and no neonates with a five-minute Apgar score ≤7 (0% vs. 7%; $p < 0.001$) compared with group B. Other pregnancy-related adverse outcomes were similar between the two groups. Inferences remained unchanged after considering different models to adjust for potential predictors of outcome.
Conclusions: LT4 therapy is associated with a decreased risk of LBW and a low Apgar score among women with SCH. This association awaits confirmation in randomized trials before the widespread use of LT4 therapy in pregnant women with SCH.

Introduction

Subclinical hypothyroidism (SCH) is a biochemical diagnosis based on a high serum thyrotropin (TSH) level with a normal free thyroxine (fT4) level. Current guidelines recommend an upper serum TSH limit of 2.5 mIU/L for the first trimester and 3.0 mIU/L for the second and third trimesters of pregnancy (1). Multiple observational studies comparing euthyroid pregnant women to those with untreated SCH have found an association of SCH with an increase in the risk of one or more adverse pregnancy outcomes, most commonly pregnancy loss, preterm delivery, gestational hypertension, and low birth weight (LBW) (2–6). However, other studies did not find any association of SCH with pregnancy complications (7–10). Publication bias may have affected these reports, as negative studies are less likely to be published. Moreover, the vast majority of the studies assessing the impact of SCH in pregnancy are at low to moderate risk of bias, warranting less confidence in their results due to small samples, imprecision in the estimates, and failure to adjust for confounding factors (11,12).

Despite the paucity of strong supportive data, the American Thyroid Association 2011 guidelines recommended levothyroxine (LT4) therapy for pregnant women with SCH and positive thyroperoxidase (TPO) antibody status (1), while the Endocrine Society in 2012 recommended LT4 therapy for all pregnant women with SCH (13). However, uncertainty remains regarding the impact of LT4 therapy on improving health outcomes in pregnant women with SCH. Taking into consideration recent studies presenting a prevalence of SCH up to 15% in the United States (14) and 28% in China (15), millions of pregnant women worldwide will be

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