Review Article

HISTORICAL AND CURRENT PERSPECTIVE IN THE USE OF THYROID EXTRACTS FOR THE TREATMENT OF HYPOTHYROIDISM

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ABSTRACT

Objective: To describe the history, refinements, implementation, physiology, and clinical outcomes achieved over the past several centuries of thyroid hormone replacement strategies.

Methods: A Medline search was initiated using the following search terms: bioidentical thyroid hormone, thyroid hormone extract, combination thyroxine (T4) and triiodothyronine (T3) therapy, homeopathic thyroid hormone therapy, and thyroid hormone replacement. Pertinent articles of interest were identified by title (and where available abstract) for further review. Additional references were identified during a review of the identified literature.

Results: A rich history of physician intervention in thyroid dysfunction was identified dating back more than 2 millennia. Although not precisely documented, thyroid ingestion from animal sources had been used for centuries but was finally scientifically described and documented in Europe over 130 years ago. Since the reports by Bettencourt and Murray, there has been a continuous documentation of outcomes, refinement of hormone preparation production, and updating of recommendations for the most effective and safe use of these hormones for relieving the symptoms of hypothyroidism. As the thyroid extract preparations contain both levothyroxine (LT4) and liothyronine (LT3), current guidelines do not endorse their use as controlled studies do not clearly document enhanced objective outcomes compared with LT4 monotherapy. Among current issues cited, the optimum ratio of LT4 to LT3 has yet to be determined, and the U.S. Food and Drug Administration (FDA) does not appear to be monitoring the thyroid hormone ratios or content in extract preparations on the market. Taken together, these limitations are important detriments to the use of thyroid extract products.

Conclusion: The evolution of thyroid hormone therapies has been significant over the extended period of time they have been in use to treat hypothyroidism. Although numerous websites continue to advocate the use of thyroid hormone extracts as a superior therapy for hypothyroidism, none of the most recent guidelines of major endocrine societies recommend thyroid extract use for hypothyroidism. **(Endocr Pract. 2015;21:1161-1170)**

Abbreviations:
AACE = American Association of Clinical Endocrinologists; **ATA** = American Thyroid Association; **BMR** = basal metabolic rate; **FDA** = Food and Drug Administration; **FT4** = free thyroxine; **131-I** = radioactive iodine 131; **LT3** = liothyronine; **LT4**= levothyroxine; **NDA** = new drug application; **PBI** = protein-bound iodine; **T3** = triiodothyronine; **T4** = thyroxine; **TSH** = thyroid-stimulating hormone; **TT3** = total triiodothyronine; **USP** = U.S. Pharmacopeia

INTRODUCTION

The human thyroid produces endogenous hormones including thyroxine ([T4] tetraiodothyronine/3,5,3',5' tetraiodothyronine]) and triiodothyronine ([T3] 3,5,3' triiodothyronine). Synthetic levothyroxine (LT4) and liothyronine (LT3) are indistinguishable from the 2 active thyroid hormones produced in the human body (1). Many popular lay

Submitted for publication October 8, 2014
Accepted for publication February 26, 2015
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Published as a Rapid Electronic Article in Press at http://www.endocrinepractice.org on June 29, 2015. DOI:10.4158/EP14477.RA
To purchase reprints of this article, please visit: www.aace.com/reprints.

See accompanying article, p. 1171.

websites and holistic practitioners (no PubMed references but 68,800 Google results on January 2, 2015) only consider the combination of LT4 and LT3 contained in pharmaceutically manufactured fixed-dose combinations and extracts from animal thyroid glands to be "bioidentical" to human thyroid hormones. It should be noted that the term "bioidentical thyroid hormones" has no widely accepted definition in the peer-reviewed literature and only 1 reference appears in a PubMed search for this term (1). Also available in this category are individually compounded pharmacy products that use commercial LT4 and LT3 (1). As FDA-approved LT4 and LT3 are both extensively reviewed elsewhere (2,3) and an in-depth review of individually compounded pharmacy products is not possible as the individual prescriptions are not FDA regulated, this review will be limited to a discussion of the history of thyroid extract products.

HISTORY OF THYROID HORMONE THERAPY USAGE

Failure of the thyroid has been recognized for centuries. The history of thyroid dysfunction and attempts to intervene is extensively reviewed by Slater and is documented as far back as 239 before the common era (BCE) in Chinese literature and in the second century of the common era (CE) in western literature (4). Initial effective treatment of thyroid disorders was linked to iodine, and there were reports of effective interventions in goiter cases (4). The Chinese are also said to have treated cretins with sheep thyroids in the sixth century CE (4). Observations by Gull published in 1873 described a disease similar to cretinism in adults that generated interest in the clinical presentation and etiology of hypothyroidism (5). The association of thyroidectomy and subsequent onset of myxedema (cachexia strumipriva) was proposed as causative in 1883 by Semon (6), who cited the report by Kocker that was presented to the German Surgical Society (4,7). This association was supported by the results of a survey of 115 surgeons (64 usable responses [56% response rate]) that were eventually published in 1888 (8). Transplantation of animal thyroid tissue into a myxedematous patient was reported in 1890 by Bettencourt and Serrano (9,10). The grafted tissue resulted in a clinical response, a nearly immediate increase in temperature, which was not associated with postoperative infection, and a positive effect on other clinical symptoms before revascularization was expected. It was assumed that the effect was due to simple absorption of tissue components (4,7). These Portuguese investigators also published the first report of subcutaneous injections with an extract of animal thyroid in 1890 (4,7,11). The use of hormones to treat hypothyroidism first appeared in the English literature in 1891 (12). In this initial report, George Murray of Newcastle-upon-Tyne described the clinical outcomes of subcutaneous injections of animal thyroid extract in a 46-year-old patient who was given the equivalent of 2.5 sheep thyroids over a few weeks (12). The next year, Murray reported clinical outcomes in 3 more patients, illustrating the visual impact of the extract treatment and documenting the first fatal cardiac complications after the initiation of thyroid hormone treatment (4,13). Subsequent reports of the action and consequences of various thyroid extracts on patient outcomes appeared (14). Early on it was noted that rapid weight loss and increases in body temperature, urine volume, and nitrogen excretion occurred when thyroid extract was administered to clinically myxedematous patients (15). As the preparation of these injectable thyroid extracts was viewed as demanding and expensive and reports of both acute and chronic complications were coming to light (4,16), the use of oral thyroid gland preparations was the next step in the development of thyroid hormone replacement. Both fresh animal thyroid tissue and extracts of animal thyroids were administered and outcomes were reported (4,17). Apparently, eating fresh sheep thyroid was not enjoyable, and the reported dosing practices were quite variable, but the use of extracts prepared in a consistent manner was considered by some to improve the consistency of outcomes (4,16-18). Soon, further observations on clinical outcomes were published, and expert dosing guidance and further cautions in regard to the potential for iatrogenic overdosage appeared (4,19). Ingestion protocols for thyroid hormone extract preparations have existed for over 110 years. It was long felt that patients would be "titrated" to clinical endpoints and considered euthyroid if feeling well and not obviously thyrotoxic. The treatment was assumed to be natural, and significant side effects had not been clearly attributed to the use of thyroid hormone. Following the adoption of oral administration of processed thyroid extract, it was common to find that patients were titrated to a clinically assessed thyroid status, where the "metabolic status" was attested to by a patient and observed by experienced physicians to represent the optimal outcome (20). Clinical parameters commonly evaluated included body weight, pulse rate, skin quality, sensitivity to cold, and quantitative measurement of Achilles tendon relaxation time (21). Eventually, adverse events associated with higher doses of ingested extract were reported, so it soon was recommended that treatment start with a low dose that should be gradually increased as required. The danger of overdosage has long been recognized (13) and has generated caution when thyroid extract is used in the elderly and those with coronary artery disease (19).

Thyroid Hormone Use Results in Advances in Understanding Thyroid Axis Physiology

The observational literature of thyroid extract use 50 years after its introduction documents interesting insights into the physiology of the thyroid regulatory system. It was noted that ingestion of desiccated thyroid by normal but

symptomatically "hypometabolic" individuals resulted in no increase in their basal metabolic rate (BMR), perhaps an initial glimpse into the nonspecificity of "hypothyroid" symptoms. However, BMR was noted to fall off precipitously for several weeks when extract ingestion ceased (22), indicating a suppression of normal thyroid function by the ingestion of exogenous thyroid hormones. Later, it was noted that increasing (supraphysiologic) extract doses could indeed raise the BMR and again after discontinuation of the supplementation, the same depression of endogenous thyroid function occurred (23). Further elucidation of the underlying physiology of the effects of thyroid extract ingestion on thyroid function was reported in 1951 by Greer, who demonstrated rapid, dose-dependent suppression of radioactive iodine 131 (131-I) uptake with increasing doses of thyroid extract, confirming gradual recovery of thyroid function as evidenced by the 131-I uptake when the thyroid extract (often alternatively referred to as desiccated thyroid or Thyroid USP) was discontinued (24).

Clinical Assessment of Thyroid Function Reveals Thyroid Extract Pharmacokinetics

Assessment of thyroid function later grew beyond thyroidal 131-I uptake, and measurement of protein-bound iodine (PBI) first reported in the 1960s became the most reliable method used in the clinical assessment and diagnosis of both hyper- and hypothyroidism (25). In the follow-up of those treated for hypothyroidism with restored BMR, it was noted that PBI concentrations varied depending on the particular thyroid hormone preparation ingested with BMR-normalizing doses of T3 associated with subnormal PBI and BMR normalized with LT4 resulting in substantial PBI elevation (25) compared to thyroid extract use (26). It was assumed that adequate replacement doses of thyroid extract returned the PBI into the expected range of euthyroid individuals. As a result of the clinician's tendency to measure blood levels to assure safe and effective dosing of thyroid hormone replacement, it had been noted that some individuals ingesting seemingly adequate doses of thyroid extract had low PBIs when using a particular manufacturer's product (25). Clinical investigation of hypothyroid subjects with 3 different thyroid extract products revealed substantial differences in the PBI values while similar clinical outcomes were observed in all (25). These studies were performed with commercial thyroid extract products available that met the contemporary U.S. Pharmacopeia (USP) standards requiring that the organic iodine content comprise 0.2 ± 0.03% of the dry weight of each product. As might be expected, there were differences in the manufacturing processes of the unique extract products produced, and it was thought that differences in the relative amounts of T4 and T3 in the products could account for the observed differences in clinical potencies relative to PBI (25). It was eventually noted that the PBI detected in the circulation of subjects taking thyroid extracts was primarily produced by the T4 content of the extract and depending on the T3 content, which was said to vary from 20 to 30 mcg per 100 mcg thyroxine content; that is, individuals titrated to a low or normal PBI might still experience thyrotoxic symptoms depending on the T3 content of the product being ingested (27). Such variability in content and outcomes led some to call for more reliable synthetic fixed-dose preparations of the T4 and T3 (28). Others attributed the variability of outcomes with thyroid extract to compliance with ingestion routines and eventually cited elevations in serum thyroid-stimulating hormone (TSH) as a more reliable indicator of inadequate and inconsistent replacement (29). Radioimmune assays were developed in the early 1970s to reliably measure both serum T4 and T3 (30). In clinical studies of euthyroid control subjects and others who were ingesting different types of thyroid hormone preparations, Surks et al measured T4 and T3 levels during the day (30). Among euthyroid controls, a pattern of constant T4 and T3 levels was evident throughout the day for both forms of circulating thyroid hormone (30). Following the ingestion of T3 alone by athyreotic subjects, dramatic increases of T3 were detected within the first 6 hours following ingestion, returning to preingestion levels 24 to 48 hours later. When athyreotic individuals ingested LT4, slight increases of circulating T4 levels occurred up to 6 hours after ingestion, but T3 levels remained constant. In hypothyroid patients ingesting thyroid hormone extract, a supraphysiologic increase in T3 level was observed in the first 10 hours after ingestion, but little if any increase in T4 was observed after extract ingestion (30). The authors concluded that the ingestion of T3 and thyroid hormone extracts were associated with increases of T3 into the thyrotoxic range for variable periods of time. They cautioned that consideration should be given to the timing of thyroid hormone ingestion and sampling to avoid confusion due to the postabsorptive peak. Additionally, the patterns of both circulating thyroid hormone levels were close to physiologic after the ingestion of LT4 alone (30).

ADVANCES IN THE CLINICAL USE OF THYROID HORMONE REPLACEMENTS

The medical literature continued the discussion of clinical experiences with thyroid hormone extracts in 1978 when Jackson and Cobb observed abnormally high T3 levels in nearly all symptomatic individuals on thyroid hormone extract who were then switched to LT4 and experienced resolution of their thyrotoxic symptoms correlated with lower T3 and higher T4 levels (31). These authors had initiated treatment in the era before reliable TSH assays and relied initially on PBI, then T4, and eventually T3 levels to titrate thyroid replacement doses. They concluded that Thyroid USP use should be discontinued as a thyroid replacement medication as it produced misleading thyroid hormone levels (low T4), which might lead to

an injudicious increase in dosage and could cause further thyrotoxicosis due to the T3 content (31). Further observations on T4 and T3 outcomes were reported in 14 pediatric patients receiving thyroid extract for hypothyroidism. While clinically euthyroid subjects were ingesting sufficient amounts of extract to maintain T4 and TSH in the normal ranges, circulating T4 levels were lower on extract than when ingesting TSH-maintaining doses of LT4, while the mean T3 levels were greatly elevated during treatment with extract (values greater than the normal range in 13/14 subjects) (32). These authors also thought that the preferred therapy for hypothyroidism should be LT4 (32). Additional pharmacokinetic observations were reported in 1982 (33). Healthy male volunteers ingested various thyroid preparations including LT4, LT3, a product called thyroglobulin, and thyroid extract tablets and underwent subsequent serial blood sampling. Serum T3 levels were pharmacokinetically identical and supraphysiologic after the ingestion of LT3, thyroid extract, and thyroglobulin products, reaching peaks 2 to 4 hours following ingestion (33). Serum T4 levels were far less responsive to the ingestion of the thyroid extracts than LT4, but T3 levels did not rise to supraphysiologic levels following LT4 preparation absorption (33). Additional reports raising concerns over the precipitation of postingestion hypertriiodothyroninemia appeared, which associated this finding with morning nervousness, palpitations, and tremor (34). The study described a 90% increase in T3 levels 3 hours after the ingestion of various doses of desiccated thyroid, resulting in supraphysiologic levels in all 21 patients evaluated (34). A strong relationship between the thyroid extract dose and the degree of T3 elevation was very clear as 6 of 7 subjects receiving 4 grains of extract or more had postabsorptive T3 levels >150 ng/dL (34). Based on these studies, calls for the "retirement" of thyroid extract preparations were common in the 1980s (34,35). One review captured the journey of thyroid hormone extracts from preparations lacking purity, standardization, and stability, acknowledging the fact that then contemporary products were vastly improved in this regard but noting that uniform biologic potencies among various preparations was not guaranteed (35). Emphasis had shifted to the comparative physiologic serum levels of T4 and T3 resulting from LT4 use compared to the predictable and substantial nonphysiologic diurnal fluctuation of T3 levels after thyroid hormone extract ingestion. Conclusions such as "desiccated thyroid possesses no uniquely desirable properties and should, therefore be retired to the place it has earned in medical history" (35) were common (34). Additional clinical reports have continued to raise concerns about thyroid extract use in older patients diagnosed with hypothyroidism. In one such publication, a 68-year-old female taking 260 mg thyroid extract daily for presumed hypothyroidism was noted to sustain a severe, reversible myocardial ischemic event associated with normal coronary artery anatomy (36). Another group reported a systematic review of thyroid hormone usage among 2,575 subjects with a mean age of 68.6 years conducted in conjunction with the Framingham Heart Study. Overall 6.9% of the population was taking thyroid hormones: 10% of females and 2.3% of males (37). These authors reported that most of the females (68%) and 55% of males taking thyroid hormones when classified as having definite hypothyroidism when symptoms, therapeutic response to thyroid hormone replacement, or elevated TSH were consistent with that diagnosis. The authors went on to classify their subjects as having probable hypothyroidism when some symptoms but no confirmatory laboratory evidence was present. Among those on thyroid medication, 69% were ingesting thyroid extract when initially seen. Over the course of the observations, several subjects were switched to LT4 by their treating community physicians, resulting a final tally of 46% on LT4 and 51% continuing with thyroid extract (37). When judging the appropriateness of indications for therapy, 20% of those on extract were judged to be ingesting the thyroid therapy for inappropriate indications compared to 0% on LT4. Definite or probable hypothyroidism was present in 81% of those treated with LT4 and 60% of those on thyroid extract, which was not a statistically significant difference (37). The authors observed that within the Framingham cohort, only 12% of females were taking thyroid hormone for inappropriate indications while 29% of the males treated with thyroid had poor indications for this intervention (37).

Most recently, the first prospective, randomized, double-blind, crossover study of clinical outcomes was conducted on 70 adult patients with primary hypothyroidism on stable doses of LT4 for at least 6 months prior to study entry (38). After baseline biochemical and neurocognitive testing, subjects were randomly assigned to either thyroid extract or LT4 therapy in identical-appearing capsules. Follow-up thyroid function testing was accomplished to assure maintenance of biochemical euthyroidism as assessed by serum TSH which, once achieved, was maintained for at least 12 weeks before cross-over to the opposite treatment (38). There was no difference in symptoms or neurocognitive function documented between the 2 therapies, but those on extract reported some weight loss, and 48.6% reported preferring the period of time they were on extract (38). Biochemically, all thyroid extract-treated patients had significantly higher total T3 (TT3) levels documented, with the highest mean values observed in those preferring LT4, while TSH levels in this LT4 preference group were not different from those on thyroid extract treatment. Those preferring extract or having no preference also had higher mean TT3 levels but also had higher TSH values, indicating that they were not thyrotoxic. Clear increases in the TT3 levels were documented 3 hours after taking the thyroid extract, but the absolute levels remained within the expected range (38).

THE PHARMACEUTICAL REGULATION OF COMMERCIAL THYROID HORMONE EXTRACT

The regulatory history of thyroid hormone products has developed in stages as the FDA has evolved as an agency. As mentioned above, treatment using extracts from animal thyroid glands have been shown to be useful since at least 1891 and were being utilized when the FDA was formed in 1906. Thyroid hormone extracts were the sole option that continued to be in general use when the Federal Food, Drug, and Cosmetic act of 1938 enhanced the FDA's regulatory authority (39). The Kefauer-Harris Amendments of 1962 were introduced in the wake of thalidomide malformations reported after use in pregnancy. These amendments required the FDA to assess the efficacy and safety of drugs introduced to the U.S. market since 1938. As thyroid extract use predated this cutoff, only thyroid hormone products introduced subsequently were subject to this higher level of regulation (39). Thyroid hormone extracts continued to be marketed as unapproved drugs without new drug application (NDA) approvals as they were only subject to previously established enforcement priorities (39). Manufacturers of extract products consider these formulations to be "grandfathered" drugs as they were distributed prior to 1938 and there have been no significant changes to the formulation, dosage form, potency, administration route, indications, or intended patient population since 1938 (39). The FDA has never formally recognized any drug as being grandfathered, but the agency recognizes that some patients firmly believe that extracts are an effective form of therapy for them. It has been speculated that as yet unidentified nonthyroid hormone-related components in thyroid extracts may account for this preference.

As such, thyroid hormone extract products are marketed as unapproved at the present time (40,41). The FDA is empowered to apply enforcement discretion upon these products, but to date, no regulatory actions have been taken. However, the agency does encourage manufacturers to submit NDAs for these products, with the focus on safe manufacturing, sterility, and limiting impurities (39,42). According to an FDA spokesman for the Division of Metabolism and Endocrinology products, to date, no enforcement actions to assure compliance with USP requirements have been taken by FDA, and no manufacturer has responded to the FDA's invitation to submit a NDA on their product (Personal Communication, Kristofer Baumgartner, Center for Drug Evaluation and Research [CDER] Trade Press office, FDA; February 2, 2015). Standardization specifications for desiccated thyroid hormone products were described in USP XVII and required that they contain not less than 0.17 and not more than 0.23% iodine content; they were also to be free of iodine in inorganic or any form of combination other than that peculiar to the thyroid gland (43). The source of thyroid material was not specified other than it was expected to be derived from domesticated animals that are used for food by humans. Initially, this standardization did not account for the known differences in goiter-suppressive capabilities of various products of porcine and bovine origin meeting the iodine standards (44,45). In addition to the species-specific differences in thyroid hormone content where the molar ratio of T4 to T3 is lower in porcine tissue compared to thyroid obtained from bovine sources (45-48), differences in the processing of tissues into pharmaceutical products result in unique thyroid hormone ratios and contents (43). From the regulators view, concerns were raised when thyroid extract preparations were on the market that appeared to meet the pharmacopeial standards based on total iodine content, but this standard was not sufficient to assure uniformity of outcomes as some of these products had little to no clinical activity (28,49-51). At the time of Stephenson's 1967 report (43), a solution to all of these variables was proposed that incorporated the use of synthetic T4 and T3 in a fixed 4:1 ratio formulation to achieve more predictable and consistent outcomes as suggested by Wool and Selenkow (20,52). Further investigations into the T3 and T4 contents of thyroid preparations continued, and in 1977 the USP standard continued to be focused on tablet iodine content (53). One study determined the T4 and T3 contents of different thyroid preparations obtained in local pharmacies. Two different forms of "Thyroid" were available, thyroid extract (Armour®, Forest Laboratories, New York City, NY) and a preparation designated as thyroglobulin (Proloid®, Warner-Chilcott, Rockaway, NJ) (53). Four different lots of 1- and 2-grain tablets of each brand were analyzed for iodine, T4, and T3 contents. The thyroid extract products had less T3 and more T4 than the thyroglobulin preparation, with T4/T3 averaging 4.3 in 1-grain tablets and 5.2 in 2-grain tablets. The thyroglobulin product was more consistent when considering the dose proportionality aspect of the USP standard as similar T4/T3 ratios of 2.9 and 2.8 in the 1- and 2-grain tablets, respectively (53). The various lots of 1-grain thyroid extract contained consistent amounts of T3 and T4, as well as a consistent T4/T3 molar ratio. However, analysis of 2-grain tablets did not have twice the T3 content as would be expected, while the T4 content was essentially twice the content of the 1-grain tablets. The T4/T3 ratio of the 2-grain tablets was therefore higher at 5.2 (53). Although standardized by identical iodine content, 65-mg thyroglobulin tablets demonstrated substantial differences in the T3 and T4 contents of products derived from bovine sources versus porcine thyroid tissue. Additionally, the molar ratios of T4/T3 were 9.1 in the bovine thyroglobulin product and 6.6 in the porcine-derived preparation (53). The authors concluded that the T3 and T4 contents of different lots of both the thyroid extract and species similar thyroglobulins were remarkably consistent, with <10% variation measured (53). Subsequently, based on several of these studies, the USP adopted new expectations for desiccated thyroid hormone product standardization in

1985 (54). Analysis of the T3 and T4 contents of thyroid extracts would require proteolytic enzymatic digestion followed by high-performance liquid chromatographic assays (55). This process set specifications for the LT3 (8.1-9.9 mcg/65 mg tablet) and LT4 (32.3-43.7 mcg/65 mg tablet) content of thyroid extract hormone products (55). This update in standardization was quite successful in assuring more predictable preparations, as manufacturers seem to have focused on these content goals in their quality control processes. Current products indicate that they provide 38 mcg thyroxine and 9 mcg triiodothyronine per each 65 mg (1-grain) tablet (www.nature-throid.com/images/Nature-Thyroid-PI-Rev041121-03.pdf, www.frx.com/pi/armourthyroid_pi.pdf). According to an FDA spokesman for the Division of Metabolism and Endocrinology products, the USP monograph is a minimal quality standard and has no effect on products coming in for approval. Knowledge of whether a manufacturer is meeting the USP expectations would rely on surveillance and inspection. The FDA could not supply evidence of this in regard to thyroid extract products and stated that to date, no independent verification of the thyroid hormone content in these products is known to the FDA (Personal Communication, Kristofer Baumgartner, CDER Trade Press office, FDA; February 2, 2015).

THYROID HORMONES IN NUTRITIONAL SUPPLEMENTS

Up until this point, we have discussed FDA recognized thyroid hormone preparations containing thyroid extracts. Reports of "epidemic thyrotoxicosis" have appeared in the literature, and a connection with the ingestion of thyroid hormone food has been postulated. The first of these reports concerned observations made in Olmstead County, Minnesota (56) but data to support a definitive linkage was weak (57). During World War II, an epidemic of nonexophthalmic thyrotoxicosis was observed in Denmark in 1941 and abated by 1945 (57). Nutritional factors were suggested as the root of this problem, but a definitive cause was not identified (57). Another report alluded to a spate of thyrotoxicosis occurring in slaughterhouse workers when the manager of a Polish meat processor prepared a special sausage with thyroid glands that had been harvested for pharmaceutical use. As the workers considered this special sausage to have "medicinal" qualities, they were given first opportunity to purchase the product and consumed most of the thyroid sausage (58). A change in procedures in April of 1983 at a midwestern slaughterhouse including abandonment of selective removal of thyroid tissue of the nearly 800 animals processed daily and a shift to a process designated as "gullet trimming" resulted in variable amounts of the animals' thyroids being included in ground beef products (59). Ingestion of this ground beef then resulted in the identification of at least 121 subjects with thyrotoxicosis that clinically resembled painless subacute thyroiditis. Analysis of products revealed the thyroid content of the meat, and a root cause analysis clarified how the ground beef had been tainted with thyroid hormones. This accidental ingestion of thyroid hormones resulted in a U.S. Department of Agriculture prohibition of gullet trimming in the processing of both beef and pork products (59). Subsequently, a further example of this type of so-called hamburger thyrotoxicosis was reported in a female living on a farm who was observed to have 5 episodes of silent thyroiditis associated with suppressed thyroglobulin levels (60). The authors of this report discovered that her family had a cow from their herd slaughtered every few years, the local butcher produced patties from gullet trimmings, and she was the primary consumer of this meat (60).

"Health-food" thyroid preparations are very popular and assumed to be safe and effective by many laypeople. Reports concerning the outcomes of ingestion of these products have been appearing with increasing frequency. A report appeared in 1986 concerning the ingestion of a weight-loss product called Enzo-caps, which was described as a natural food product derived from papaya, garlic, and kelp (61). This product had been manufactured in Peru and imported to the U.S. as a nutritional supplement. Classic symptoms of thyrotoxicosis were observed along with elevations of both T4 and T3 that were associated with suppressed RAI uptake. Biochemical analysis of the product revealed both LT4 and LT3 in variable amounts and ratios among different capsules obtained from individuals at different times (61). If taken as suggested at 4 capsules daily, this product, which was only briefly available, would deliver up to 44.4 mcg T3 and nearly 450 mcg LT4 daily (61). In 1989, the case of a patient with hypothyroidism was detailed that exposed the sometimes cryptic nature of thyroid hormone ingestion when "supplements," considered safe and natural by laypeople, resulted in diagnostic confusion and thyrotoxicosis (62). After documentation of primary hypothyroidism following the discontinuation of all FDA-approved thyroid hormone products, the patient's preference for and ingestion of "natural" remedies for his hypothyroidism resulted in variable thyroid function test outcomes on several different products labeled to indicate that thyroxine had been removed. Eventually, frank thyrotoxicosis resulted when recommended doses of 1 such product were ingested (62). The authors went on to report that they had identified 3 such products in Boston area health-food stores, 1 of which was cryptically labeled as having "preserved natural constitutes" that were actually more expensive than standard FDA-approved extracts and thyroxine products (62). This experience extends into the present as reported by Hoang et al, who noted a patient with thyroid extract-induced thyrotoxicosis after ingesting a thyroid supplement. As all clinical and biochemical thyroid abnormalities resolved with supplement discontinuation, the authors concluded that the thyrotoxicosis

was supplement induced (63). A recent internet search verifies that 1 of these products is currently available. The iHerb.com website shares 27 anecdotal experiences of rapid and miraculous changes in clinical symptoms resulting in a 4.5/5-star rating for this product (www.iherb.com/product-reviews/Natural-Sources-Raw-Thyroid-60-Capsules/6009/?p.....). More recently, 2 reports appeared in 2013. One case report described a patient with an apparent history of recurrent episodes of silent thyroiditis with spontaneous resolution (64). During a subsequent episode, an elevated total T3 level was observed while the serum thyroglobulin was suppressed, which initiated a search for an exogenous thyroid hormone source. The patient eventually admitted to intermittent use of a weight-loss supplement called Talla Baja vitamins, which were subsequently found to contain 100 mcg LT3 per pill (64). Kang et al analyzed the thyroid hormone content of 10 readily available health supplements promoted to provide "thyroid support" (65). The amounts of thyroxine and triiodothyronine were determined for each product, and the dose of each was calculated for individuals consuming the recommended number of pills. Ninety percent of the products contained LT3 with amounts up to 25 mcg T3 per tablet observed, while 50% of the products contained thyroxine in doses greater than 22 mcg/tablet (65). Taken as directed, 50% of the supplements delivered more than 10 mcg of T3 daily and 40% supplied up to 91.6 mcg T4 daily (65). Unexpected potency of compounding pharmacy preparations due to errors of proportion also can lead to unexpected, potentially fatal thyrotoxic outcomes. This was noted in a case report of thyroid storm resulting from a massive compounded overdose of both LT4 and LT3 which finally responded to plasmapheresis (66) and a series of hospitalizations (1 death) in patients dispensed capsules containing milligram doses of LT4 when microgram amounts had been prescribed (67). This also occurs in other settings as highlighted in a recent report of 18 patients (1 fatality) admitted to the hospital following the use of compounded diet pills that contained 30 mg thyroxine rather than the intended 25 mcg (68). These findings demonstrate further issues associated with the non-FDA regulated application of thyroid hormones.

RECOMMENDATIONS FOR CLINICAL USE

None of the recently published guidelines for thyroid hormone replacement therapy endorse the use of thyroid hormone extracts as preferred therapy; rather, they all discourage its use (2,69-71). Despite these documented issues with thyroid hormone extracts, advocates for the use of these products hold firm to the stance that thyroid extracts are superior to LT4 products in the treatment of both traditionally diagnosed and "sublaboratory" forms of hypothyroidism and other conditions (72). Others view the use of thyroid hormone extracts as an alternative to the use of LT4 and LT3 combination therapy (73,74) for patients with documented hypothyroidism, although the ratio of T4 to T3 in desiccated thyroid products is different from human thyroid output and many of the experimental protocols have unsuccessfully attempted to prove that this combination therapy is superior to LT4 alone (75).

National Guidelines on Thyroid Hormone Extract Use

Recommendations on the use of thyroid hormones in the treatment of hypothyroidism have been made by national organizations based on the consensus of topic expert panels. The 2011 Guidelines of the American Thyroid Association (ATA) for the Diagnosis and Management of Thyroid Disease during Pregnancy and Postpartum recommend (Recommendation #10) that treatment of maternal hypothyroidism is with the administration of oral levothyroxine. It is strongly recommended not to use other thyroid preparations such as LT3 or thyroid extract (76). Similarly, the clinical practice guidelines cosponsored by the American Association of Clinical Endocrinologists (AACE) and the ATA recommend (Recommendation #22.3) that LT4 and LT3 combinations should not be administered to pregnant women or those planning pregnancy (2). The AACE/ATA guidelines go on to state that there is no evidence to support using thyroid extract in preference to LT4 monotherapy in the treatment of hypothyroidism; therefore, thyroid extract should not be used for the treatment of hypothyroidism. Still, the group did acknowledge that LT4/LT3 combination therapy was an avenue of future research (2). The LT4 monotherapy preference has been echoed by the current Latin American Thyroid Society (70), and the most recent ATA update also found insufficient evidence to recommend the addition of LT3 to LT4 monotherapy outside of clinical trials (70,71). European consensus groups, while clearly stating that LT4 is the standard treatment of hypothyroidism, have suggested that the use of T4/T3 combinations as an experimental approach to address the subjective complaints of compliant LT4-treated patients should be considered. They go on to caution that subjects should receive appropriate support to deal with the chronic nature of their disease, and that appropriate steps be taken to rule out associated autoimmune disorders. A suggested LT4/LT3 ratio of 13-20:1 is recommended, but products with lower ratios such as thyroid hormone extracts (4:1) are not recommended (69). Patient advocacy groups continue to promote the empowerment of patients to seek alternative treatments for hypothyroidism, specifically LT4/LT3 combinations including desiccated pig thyroid (thyroid extract), which they have justified by citing the European guidelines cited above (77).

CONCLUSION

Thyroid hormone therapy preparations come in numerous forms but should in no case contain hormones

other than LT4 and LT3 as their active ingredients. LT4 monotherapy is overwhelmingly recommended as the best proven therapeutic approach to patients with hypothyroidism. Thyroid hormone extracts and fixed synthetic combinations containing LT4 and LT3 deliver supraphysiologic doses of T3 and are not generally recommended as first-line therapy for hypothyroidism. The clinician must remember that unpredictable amounts of both hormones may also be contained in unregulated dietary supplements derived from animal thyroid tissues, which may result in alterations in thyroid status depending on the supplement contents. Finally, compounding pharmacies are capable of mixing commercially available LT4 and LT3 into any number of ratios, concentrations, and time-release formulations according to individual physician prescriptions. These compounded preparations are neither FDA-approved nor regulated, so no prospective, peer-reviewed data is available to assess the clinical outcomes with these custom therapies.

DISCLOSURE

The author previously acted as a scientific consultant for Veracyte Inc, Akrimax Pharma, Abbott Labs, and Sandoz Pharma and served as the Content Director at PriMed (2013 and 2015). He is a Board Member of the AACE New England Chapter and serves on the Editorial Boards of *Thyroid* and *Endocrine Practice*. The Author is also a member of the Board of Directors of the American Thyroid Association. The opinions expressed are the personal opinions of the author and do not represent any official position of the American Thyroid Association.

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