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Emerging Therapies in Hypothyroidism

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Abstract

Levothyroxine (LT4) is effective for most patients with hypothyroidism. However, a minority of the patients remain symptomatic despite the normalization of serum thyrotropin levels. Randomized clinical trials including all types of patients with hypothyroidism revealed that combination levothyroxine and liothyronine (LT4+LT3) therapy is safe and is the preferred choice of patients versus LT4 alone. Many patients who do not fully benefit from LT4 experience improved quality of life and cognition after switching to LT4+LT3. For these patients, new slow-release LT3 formulations that provide stable serum T3 levels are being tested. In addition, progress in regenerative technology has led to the development of human thyroid organoids that restore euthyroidism after being transplanted into hypothyroid mice. Finally, there is a new understanding that, under certain conditions, T3 signaling may be compromised in a tissue-specific fashion while systemic thyroid function is preserved. This is seen, for example, in patients with metabolic (dysfunction)-associated fatty liver disease, for whom liver-selective T3-like molecules have been utilized successfully in clinical trials.

INTRODUCTION

Hypothyroidism is a condition caused by insufficient secretion of thyroid hormones (TH). In most cases, this can result from genetic defects in the thyroid gland, surgical thyroidectomy, thyroid gland ablation with ^{131}I, or autoimmune destruction of the thyroid gland (1). It can also be the result of accelerated clearance of TH, beyond what the thyroid gland can compensate for by increasing thyroid secretion (2). In patients with hypothyroidism, the circulating levels of TH drop and remain subnormal, causing insufficient TH signaling within tissues (the plasma and tissue pools of TH are in equilibrium). The ensuing overall disruption in the expression of genes that are normally responsive to TH is what underlies the clinical signs and symptoms that we recognize in patients with hypothyroidism, affecting mood, cognition, and metabolism. If left untreated, hypothyroidism may become a debilitating disease and eventually lead to death.

For the most part, the standard of care for the treatment of hypothyroidism is to restore TH levels with the intent of normalizing the tissue content of TH and the expression of TH-responsive genes in all tissues (3). The strategies to accomplish this evolved since the nineteenth century and included heterologous and autologous thyroid transplant, subcutaneous injection of animal thyroid extract (or simply rubbing it on the skin), eating lightly cooked animal thyroid (purchased weekly from a butcher), and finally taking tablets containing desiccated thyroid extracts (DTE). In the decades that followed DTE, tablets containing levothyroxine (LT4) extracted from animal thyroid and tablets of synthetic TH, i.e., LT4 and/or liothyronine (LT3), also became commercially available (4). Up until the late 1960s, in each therapeutic modality, the doses were adjusted clinically, with the primary goal of resolving symptoms. Physicians prescribed as much TH replacement as possible, managing a balance between resolving symptoms and avoiding thyrotoxicosis. Later, the development of the assay to measure serum thyrotropin (TSH) levels greatly simplified this task and reduced the average dose of TH replacement (4).

Daily tablets of DTE were effective in treating hypothyroidism in children, adults, and pregnant women, but there were complaints about inconsistent potency among brands. Also, synthetic LT4 and/or LT3 were only used in a minority of the cases because both molecules exhibited similar effects and their relationship was not fully understood; neither one normalized plasma levels of protein-bound iodine, an earlier method to estimate TH levels in the circulation. The discoveries that humans can activate the prohormone T4 to biologically active T3 molecule outside the thyroid gland, and that the plasma of LT4-treated thyroidectomized patients contains substantial amounts of T3, were interpreted to mean that the body is capable of producing the necessary amounts of T3 as long as sufficient amounts of T4 are provided. This finding obviated the use of LT3 in the treatment of hypothyroidism and elevated LT4 to become the standard of care worldwide (4).

The change to therapy with LT4 was introduced without formal randomized controlled trials (RCTs) to test the effectiveness and safety of LT4. Common sense, practical aspects (such as color-coded tablets with multiple doses), and studies with limited patients supported the unanimous recommendation by professional societies of LT4 as the standard of care for the treatment of hypothyroidism. Indeed, by many measures, this has been a success story. Treatment with LT4 proved to be safe and to resolve symptoms of overt hypothyroidism. Its utilization is straightforward, and patients can be managed long-term by internists and advanced practice providers with minimal involvement of endocrinologists (4).

For some patients, however, the success story was limited by the persistence of residual cognitive symptoms and decrements in the quality of life (5–7). Many patients also complained of difficulties managing body weight (8) and exhibited elevated serum cholesterol levels (9) despite higher statin utilization (10, 11); some of these patients resisted the switch from DTE to LT4. These findings were interpreted by some as evidence that the T3 content in the DTE tablets

could play an important role in the treatment of hypothyroidism. Indeed, physicians in the United Kingdom and the United States concluded back in the 1960s that only treatment with LT4+LT3 was able to resolve symptoms and restore TH levels (as assessed through protein-bound iodine levels) (12–14). These anecdotal observations (and the limited clinical studies) led to scores of RCTs in the 1980s and 1990s that compared therapy with LT4+LT3 versus LT4 for 6–12 months. By and large, both were proven to be effective and safe in the treatment of hypothyroidism. The fact that patients preferred LT4+LT3, as evidenced in two recent meta-analyses (15, 16), was not sufficient to challenge the standing of LT4 as the standard of care. The persistence of residual symptoms, along with three key scientific discoveries in the 2010s, reawakened interest in therapy containing LT3 for hypothyroidism.

The first discovery was that maintaining normal plasma T3 levels is the main directive of the hypothalamus-pituitary-thyroid (HPT) axis (17). The creation of genetically modified mice with inactivation of the deiodinase genes (mice that are not capable of extrathyroidal conversion of T4 to T3) led to the unexpected observation that in these mice the serum T3 levels remained normal, even in the absence of all deiodinases. Thyroid production of T3 is increased and the HPT axis tolerates elevated serum T4 and TSH levels to preserve serum T3 levels. This was first observed in 2007 (18) and later confirmed by other laboratories (19). A similar scenario is observed in individuals with mild or moderate iodine deficiency. Serum T4 levels are low, and TSH levels are high, but serum T3 levels remain within the normal reference range (20).

The second discovery was that patients with hypothyroidism kept on LT4, with a normal serum TSH, exhibit a relative (and sometimes absolute) deficiency of T3. This was first observed in 1974 (21) and was confirmed by other groups in studies involving thousands of patients (22), but unfortunately was dismissed by clinical guidelines (23). Adding to the controversy, a minority of the studies were not able to detect a difference between controls and LT4-treated patients (24), but given the intrinsic variability of the T3 assay, these studies might not have been properly powered to detect the ~15% reduction in the LT4-treated group. The mechanistic basis for the relative T3 deficiency in LT4-treated patients was subsequently elucidated. Due to tissue-specific mechanisms that regulate the local conversion of T4 to T3 (ubiquitination of the type 2 deiodinase, D2), T4 is very effective in triggering the pituitary feedback mechanism and normalizing serum TSH levels. In contrast, T4 is not nearly as good at normalizing serum T3 levels (D2 is inactivated by T4), hence the T3 deficiency in the setting of normal serum TSH levels (25, 26).

The third discovery was that patients with the Thr92Ala polymorphism in *DIO2*, the gene encoding D2, exhibited better clinical outcomes when treated with LT4+LT3 as opposed to LT4 alone (27). Later, this polymorphism was found to be associated with an approximately 40% reduction in the catalytic activity of D2 (28, 29), and a mouse carrying the *DIO2* polymorphism exhibited signs of reduced T3 signaling in the brain that responded to therapy containing LT4+LT3 (28). The proposed role played by the Thr92Ala *DIO2* polymorphism was not reproduced in all populations (30). However, more recent studies with a larger number of subjects confirmed the association between the *DIO2* polymorphism and the reduced effectiveness of LT4. These observations led to the idea that compounding factors such as genetic background and comorbidities might impair even further the effectiveness of therapy with LT4, leading to residual symptoms despite the normalization of serum TSH levels (31).

Currently, the American, British, and European Thyroid Associations, as well as the Society for Endocrinology, agree that therapy with LT4 might leave a substantial number of patients with residual symptoms of hypothyroidism (32, 33). They also agree that serum T3 levels might not be restored in all patients, even when serum TSH and free T4 levels have been normalized (32). Both points are critically important because they have not been sufficiently emphasized among physicians.

There is no road map for what to do next, given the paucity of clinical trials with these patients. It seems common sense to confirm the diagnosis of hypothyroidism and proceed with a clinical and laboratory workup to exclude comorbidities that can lead to hypothyroid-like symptoms (34, 35). Once this is done, the four professional societies recommend a trial with LT4+LT3 (32). As a result of these changes in the clinical guidelines, the number of patients on combination therapy has doubled in the last 10 years (36). Currently, it is estimated that in the United States, about 1.4 million patients are on DTE and 400,000 patients are on a combination of synthetic LT4 and LT3.

The goal of this article is to review the most recent studies involving therapies in the treatment of hypothyroidism. We searched PubMed and Google Scholar for studies using the keywords "liothyronine," "desiccated thyroid extract," "thyroid organoids," or "slow release T3," published between January 2020 and February 2023. We also reviewed the topic "treatment of hypothyroidism" in textbooks published between 1850 and 1980. Readers are referred to other excellent reviews on this topic for completeness and alternative views (37–41).

THERAPY WITH LT4

For over 50 years now, LT4 has been the standard of care for the treatment of hypothyroidism (39). Although regulatory agencies such as the US Food and Drug Administration did not require an RCT for the full approval of LT4, there is overwhelming evidence that LT4 restores clinical and biochemical euthyroidism in the vast majority of patients with hypothyroidism. Thus, it stands to reason that LT4 should remain the standard of care for the treatment of hypothyroidism (3). A caveat is that LT4 is not 100% effective in restoring clinical euthyroidism in all patients with hypothyroidism, despite the normalization of serum TSH levels (32). Given that hypothyroidism affects millions of patients, even if therapy with LT4 is minimally ineffective, the deficit ends up impacting a substantial number of patients. With that in mind, new approaches are being developed for these patients and are considered in this article.

THERAPY WITH LT4+LT3

The candidate patient for combination therapy has been treated with LT4 and maintains a normal serum TSH level but still exhibits residual symptoms of hypothyroidism (32). Other inclusion and exclusion criteria, as well as practical approaches to start patients on combination therapy, have been discussed extensively elsewhere (34). The basic principle to transitioning patients who have been on a stable dose of LT4 (with normal serum TSH levels) to LT4+LT3 is to reduce the dose of LT4 and introduce an equivalent dose of LT3. Multiple T4:T3 ratios have been tested, and formulas have been developed to calculate an initial T4:T3 ratio (35, 42). A reasonable starting point is an LT4:LT3 dose ratio similar to what is found in the human thyroid gland, which ranges between 13:1 and 20:1. For example, if a patient maintains a normal serum TSH on 100 μg of LT4/day, then the dose of LT3 is calculated by dividing 100/20 = 5 μg. This dose is split into two daily doses, the second ~8 h after the first or 1–2 h before dinner. The new dose of LT4 will be 100 μg minus the dose of LT3 × 3 [100−(5 × 3) = 85 μg] (round off 88 μg). Thus, a patient on LT4 100 μg daily can be switched to LT4 88 μg daily plus LT3 2.5 μg twice daily.

In our experience, such formulas have value as an initial approach that invariably is followed by minor adjustments in the doses of LT4 and LT3 based on symptoms and serum TSH and TH levels (which should be kept within the normal range).

Effectiveness

An undisputed result of combination therapy with synthetic LT4 and LT3 or with DTE is the normalization of the serum free T4 levels (which are relatively higher in LT4-treated patients)

and serum T3 levels (which are relatively lower in LT4-treated patients). Replacement doses of synthetic or natural hormones can be titrated to promote these changes without suppressing serum TSH levels (43–47). Notwithstanding, the question of whether this is effective in decreasing residual symptoms of hypothyroidism remains controversial.

During the last 50 years, scores of clinical trials have compared the effectiveness and safety of LT4 monotherapy versus LT4+LT3 combination therapy in the treatment of hypothyroidism (48). By and large, these trials have concluded that both therapies are equally effective in resolving symptoms of overt hypothyroidism and normalization of serum TSH levels. This is yet another critical point that has not been sufficiently emphasized among physicians. A recent meta-analysis of 18 RCTs comparing LT4+LT3 versus LT4 for adult patients with hypothyroidism examined clinical outcomes and patient preferences (16). The authors obtained low- to moderate-certainty evidence that no differences exist in treatment effect between therapies regarding clinical status, quality of life, psychological distress, depressive symptoms, and fatigue. A second meta-analysis of these 18 studies (883 patients) also concluded that compared with LT4 monotherapy, LT4+LT3 combination therapy was equally effective in improving psychological health (15). Last, both analyses concluded that patients significantly preferred LT4+LT3 (16).

A caveat associated with these RCTs is that they might not have enrolled large enough numbers of patients who remained symptomatic while on LT4 (32). The American, British, and European Thyroid Associations recommend that future trials be focused on symptomatic LT4-treated patients (32). Considering that symptomatic patients represent only 10–20% of the total population of patients with hypothyroidism, it is unlikely that any of these trials was sufficiently powered to detect differences between therapy with LT4 versus LT4+LT3 for those symptomatic patients. In other words, asymptomatic LT4-treated patients (the vast majority) are unlikely to benefit from combination therapy, and their results would certainly dilute any beneficial effect experienced by the symptomatic patients.

A hint that this is indeed the case was obtained in a recent crossover RCT comparing therapy with LT4, LT4+LT3, and DTE (43). When the whole group of 75 patients was analyzed, no differences were observed among the three different therapies. However, when the analysis was broken down according to the intensity of symptoms while on LT4, it became clear that only those patients with the highest level of symptoms while on LT4 benefited from either LT4+LT3 or DTE. An open-label study of consecutive symptomatic LT4-treated patients supported the benefits of combination therapy (49).

Safety

Synthetic T3 or the T3 contained in DTE is rapidly absorbed through the gastrointestinal (GI) tract after oral administration. Two to three hours after administering a T3-containing tablet, serum T3 will reach a peak level that depends on the baseline (fasting) values and the dose of T3 administered. T3 is also rapidly metabolized through inner ring deiodination to 3,3′-T2, with a half-life of 12–24 h. As a result, serum T3 will drop rapidly after the peak level has been reached and return to baseline values (immediately before a new tablet is administered) (48). It is estimated that in a patient taking 87.5 μg LT4 daily, the delta between the lowest and highest T3 levels is ∼25 μg/dL after each of two daily doses of 3.25 μg LT3, ∼40 μg/dL if the doses are 5.0 μg LT3, and ∼75 μg/dL if the doses are 10 μg LT3 (50). Nonetheless, in none of these scenarios did T3 levels in the circulation cross the upper limit of normal.

Given the well-known effects of T3 on the cardiovascular and musculoskeletal systems, these potentially life-long swings in serum T3 levels have concerned physicians preparing clinical guidelines when considering therapy containing LT3 or T3 (3). This is understandable. However, to our knowledge, not a single study has been published in which T3-containing treatment for

hypothyroidism, in patients who keep normal serum TSH levels, has been associated with negative skeletal or cardiovascular outcomes. On the contrary, analysis of 18 RCTs found that similar proportions of adverse events or reactions were observed between LT4 and LT4+LT3 treatment groups (16).

To identify adverse outcomes for LT3-treated patients, cardiovascular and bone health outcomes were the focus of an observational study (1997–2014) in the Scottish region of Tayside (51). The total follow-up was 280,334 person-years with a mean follow-up of 9.3 years (standard deviation 5.6) and a maximum follow-up of 17.3 years. No increased mortality or morbidity risk due to cardiovascular disease, atrial fibrillation, or fractures after adjusting for age was observed in those patients using LT4+LT3 ($n = 327$) or LT3 alone ($n = 73$) when compared with the nearly 34,000 patients taking only LT4; the number of prescriptions for bisphosphonates or statins was similar among groups. Similar findings were obtained in Sweden after all-cause mortality was compared between 500,000 patients taking LT4 and 11,000 patients on therapy containing LT3 (52). Notwithstanding, a Korean study of 1,500 patients did find an association between the use of LT3 and heart failure and stroke, but the study did not provide LT3 doses, nor serum TH or TSH levels (53).

The frequency of adverse events and reactions among patients taking LT4, LT4+LT3, or DTE was similar in two single-center crossover RCTs involving ~150 patients (43, 44). In a recent multicenter prospective RCT that compared 141 LT4-treated patients with 143 DTE-treated patients with a mean age of 54 years for almost 1 year, the frequency of adverse events was similar in both (parallel) arms (45, 46).

DEVELOPMENT OF SLOW-RELEASE T3

While the multiple RCTs and large retrospective studies show that therapy containing T3 is as safe as therapy with LT4, the 2014 American Thyroid Association clinical guidelines for the treatment of hypothyroidism called for the development of new T3 formulations that would avoid the swings in serum T3 levels observed with the current T3-containing formulations, i.e., LT3 or DTE. Examples of potential formulations that could be developed include slow release, slow absorption, or slow production of T3 molecules.

One of the earliest approaches to develop slow-release T3 formulations was the utilization of tablets containing modified matrix systems made with hydroxypropylmethylcellulose, sodium carboxymethylcellulose, calcium phosphate, and magnesium stearate. Other combinations of salt and matrices have also been tested, including mannitol, magnesium stearate, calcium phosphate, and microporous polypropylene (US Patent #5,324,522). When tested in vitro, the rate of T3 release from such capsules could be modulated according to their content and grade of methyl cellulose and other excipients (54). In clinical trials, slow-release LT3 tablets were given to 17 hypothyroid individuals, and the results confirmed a slightly slower release of LT3 in the intestine and a less prominent peak T3 in the serum (by ~9%) at a later time (from ~3.2 to 5 h) (55). However, sustained serum T3 levels were not observed with other formulations prepared with microcrystalline cellulose and magnesium stearate (BCT303) (56). These results are important because they illustrate the difficulties in preparing slow-release LT3 formulations while utilizing matrix systems. It is important to note the commercial availability of the so-called slow-release LT3 formulations prepared by compounding pharmacies. To our knowledge, these claims are based on in vitro studies and have not been documented in clinical trials.

In a totally different approach, investigators clinically tested two modified T3 molecules, T3-sulfate and poly-zinc-LT3. The first molecule takes advantage of the fact that the phenolic hydroxyl within the T3 molecule can be sulfated (T3-S), a reaction that inactivates T3 but

dramatically enhances its solubility in water and loss to the environment (57). At first, it was thought that T3-S taken orally could not be absorbed through the GI tract, but subsequent studies demonstrated that it is readily absorbed into the portal system and the systemic circulation (58). Its great advantage lies in the fact that the liver contains sulfatases that can slowly reactivate T3-S via desulfation, "secreting" T3 back into the circulation (59). Some bacteria in the GI tract can also reactivate T3-S to T3, adding to the overall production of T3 from T3-S.

Preclinical studies done in hypothyroid rats revealed that T3-S administered through gavage could be converted back to T3 and was capable of triggering systemic thyromimetic effects (60). Next, clinical studies were conducted in thyroidectomized individuals given T3-S orally. Circulating T3-S reached a peak level between 3 and 4 h. At the same time, T3 levels (generated through T3-S desulfation) increased rapidly in the circulation, with a peak between 2 and 4 h that was followed by a variable plateau that lasted for up to 48 h and depended on the dose of T3-S administered. These findings indicated that patients could convert sufficient amounts of orally administered T3-S into T3; hence, T3-S could potentially be used in the treatment of hypothyroidism to restore T3 levels without major swings in T3 levels (61).

The next phase in the development of T3-S was to study thyroidectomized patients receiving 100–150 μg LT4 of which 25 μg LT4 was replaced with 40 μg T3-S (62). As expected, a significant reduction in mean T4 values was observed with no variations in serum T3 levels. No adverse events related to experimental treatment were observed, and no patients discontinued the treatment. These results are promising, and they indicate that LT4+T3-S in patients with hypothyroidism may allow the maintenance of normal and steady levels of serum T3, with the restoration of a physiological free T4:T3 ratio (62). The use of T3-S remains an ingenious strategy that should be pursued further.

The other viable slow-release T3 candidate molecule utilizes metal coordination, which results in T3 polymers with zinc, i.e., poly-zinc-LT3. This copolymer of zinc and T3 forms a supramolecular complex that has mucoadhesive properties, which, when coupled with its hydrolysis behavior, make it a slow-release formulation of T3 (63). If we consider poly-zinc-LT3 as a prodrug, then the process of modified drug release and absorption should involve three distinct steps: (*a*) mucoadhesion to an area of the GI tract, then (*b*) controlled ligand exchange (e.g., hydrolysis) of T3 from poly-zinc-LT3, followed by (*c*) LT3 absorption. Of note, zinc is an essential mineral involved in multiple physiological functions, and the amount contained in a 30-μg dose of poly-zinc-LT3 is <1/1,000 of the daily recommended allowance.

Capsules of poly-zinc-LT3 were first given to hypothyroid rats via oral gavage, and blood samples were obtained during the next 24 h. Remarkably, the serum T3 levels exhibited favorable pharmacokinetics (PK) (63), i.e., an approximately 30% lower peak (lower Cmax) that was delayed (longer Tmax) by ~6 h as compared to serum T3 levels in rats given equimolar amounts of LT3. The T3 clearance rate did not show differences between poly-zinc-LT3- and LT3-treated rats. TSH levels, which were elevated, declined rapidly after LT3 administration, but the decline was delayed by ~4 h in poly-zinc-LT3-treated rats. Daily administration of poly-zinc-LT3 for 8 days showed pharmacodynamics similar to LT3 treatment in rats, such as reduction of serum cholesterol, restoration of growth rate, and induction of T3-dependent genes in the heart, liver, and brain (63).

In a first-in-human trial, a crossover RCT tested poly-zinc-LT3 in healthy volunteers to define the PK of poly-zinc-LT3-derived T3 after a single dose, describe the pharmacodynamics of poly-zinc-LT3-derived T3, and compare the occurrence of adverse events versus placebo or equimolar doses of LT3 (64). Blood samples were collected for the next 48 h. While LT3-derived serum T3 levels exhibited the expected profile, with a Tmax at ~2 h and return to basal levels by 24–36 h, poly-zinc-LT3-derived serum T3 levels exhibited an approximately 30% lower Cmax that was

delayed by 1 h and extended into a plateau that lasted up to 6 h. This was followed by a lower but much longer plateau; by 24 h, serum T3 levels still exceeded half of Cmax. Remarkably, the areas under the curves were similar, indicating that similar amounts of T3 were absorbed but with substantially different PK. TSH levels were similarly reduced in both groups (64). These data indicate that poly-zinc-LT3 possesses the necessary properties to achieve an improved T3 PK, with stable levels of serum T3.

REGENERATIVE APPROACHES

A heterologous (and subsequently autologous) thyroid transplant was the first approach to treat patients with hypothyroidism (4). Transplantation never worked, but a temporary improvement of the condition was observed due to the large amounts of TH contained in the transplanted organ. With the development of organoid culture technology, the field of regenerative medicine has studied many types of organs, including the liver, intestine, pancreas, kidney, skin, and thyroid gland (65). Using mouse embryonic stem cells (ESCs), primordial lung and thyroid progenitors were obtained by manipulating the transforming growth factor β, bone morphogenic protein, and fibroblast growth factor signaling pathways (66). The subsequent overexpression of the transcription factors NKX2.1 and PAX8 (67) led to fully differentiated follicular cells that express thyroid-specific genes such as TSH receptor, sodium/iodide symporter, and thyroglobulin. Exposure to human TSH causes these cells to organize in a 3D follicular architecture that was grafted under the kidney capsules of hypothyroid mice. Four weeks later, T4 levels became detectable and serum TSH levels were reduced when compared to levels before grafting (67).

In subsequent studies (68), thyroid progenitors derived from mouse ESCs were matured into thyroid follicular organoids that provided functional secretion of TH in vivo and rescued hypothyroid mice after transplantation. More recently, transplantable thyroid organoids derived from human ESCs restored plasma TH levels in athyreotic mice (69). These studies suggest that thyroid organoids have a strong regenerative capacity in vivo and provide the proof of concept for future therapeutic development (69).

An additional ingenious approach was recently developed (70) in which porcine thyroid cells were microencapsulated in alginate-poly-L-ornithine-alginate semipermeable microcapsules that exchanged TH and TSH with the surrounding tissues but prevented the passage of immunoglobulins and host cells that mediate the immune response. Upon stimulation with TSH, these cells formed 3D follicular spheres that released TH (70). Given the initial success, it is conceivable that the microencapsulation technology could be combined with organoids for in vivo transplantation of human thyroid organoids. Of note, similar approaches with pancreatic islet xenotransplantation are not yet durable, in part because of eventual increases in the levels of circulating proinflammatory cytokines associated with reduced graft viability (71, 72).

TISSUE-SPECIFIC RESTORATION OF T3 SIGNALING

While hypothyroidism is a systemic disease, there are circumstances in which a reduction in TH signaling can be localized, restricted to a specific organ. For example, there is considerable evidence that a high-fat diet can reduce the expression of transcriptional regulators that are necessary for T3 signaling in the liver (73–75). Furthermore, the study of surgical liver biopsies of obese individuals identified sets of downregulated genes previously demonstrated to be positively regulated by T3 (74). This could be critically important given that TH activates autophagy in the liver and stimulates fatty acid β-oxidation and oxidative phosphorylation (76). These data suggest that impaired TH action may play a role in the altered patterns of gene expression in fatty liver and contribute to the establishment of steatosis and fibrosis. Indeed, low-dose LT4 reduces

intrahepatic lipid content in patients with type 2 diabetes mellitus and metabolic (dysfunction)-associated fatty liver disease (77), whereas the opposite is observed in patients with resistance to TH (78).

There are two TH receptor genes expressed throughout the body, and the liver expresses predominantly the gene encoding THRβ. This observation inspired the development of T3-like molecules with selective binding to each receptor isoform (79). Thyromimetics that target the liver and/or THRβ have been developed and used to prevent and/or treat hepatosteatosis and nonalcoholic steatohepatitis (NASH). These molecules have reduced effects on the brain and the cardiovascular and musculoskeletal systems, given their selectivity for the THRβ isoform versus THRα. VK2809, a liver-specific THRβ agonist, decreased hepatic triglyceride levels in mice by simultaneous restoration of autophagy, mitochondrial biogenesis, and β-oxidation of fatty acids (80). Resmetirom (MGL-3196), another liver-specific THRβ agonist, was used in humans for the treatment of NASH in a multicenter RCT; it was found to decrease hepatic fat content after 12 and 36 weeks and could potentially reduce hepatosteatosis and NASH (81). Restoring TH signaling in the liver with liver-specific thyromimetic drugs represents a potential therapy for hepatosteatosis in nonalcoholic fatty liver disease.

A unique strategy for directing T3 to the liver included engineered chemical conjugates of glucagon and T3, resulting in the delivery of T3 to the liver (the liver selectively expresses high levels of glucagon receptors) (82). This property directed the hybrid molecule to the liver while sparing the cardiovascular system from adverse T3 effects. Treatment with this conjugate corrected hyperlipidemia, steatohepatitis, atherosclerosis, glucose intolerance, and obesity in mouse models of obesity. These findings support the strategy of fusing T3 to a second hormone in a single molecular entity in order to obtain tissue-specific effects of T3 (82).

CONCLUSION

LT4 treatment of patients with hypothyroidism does not restore normal TH homeostasis. While this does not seem to be a problem for most patients, about 10–20% of the patients do not fully benefit from treatment with LT4 and may improve with the combination of LT4 and LT3. LT3 is commercially available as a sodium salt, which results in rapid duodenal availability and absorption. More than 20 prospective RCTs comparing LT4+LT3 versus LT4 proved the combination to be safe and effective. Safety was also confirmed in retrospective population-level analyses. Prompted by professional guidelines, pharmaceutical companies are working on the development of slow-release formulations of LT3 and on new strategies to enhance T3 signaling in a tissue-specific fashion. Thyroid organoids that can be easily transplanted and are capable of restoring TH levels in thyroidectomized mice have also been developed. While this wave of new approaches and technologies is exciting and promising for the near future, we should bear in mind that rapidly absorbed LT3 is commercially available now and, as recommended by clinical guidelines, can be used safely to improve the lives of millions of patients with hypothyroidism who exhibit residual symptoms while on LT4 therapy.

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