Commentary

A MUCH-NEEDED HISTORIC PERSPECTIVE ON THE THERAPEUTIC USE OF THYROID HORMONES

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In this issue of *Endocrine Practice*, Hennessey (1) brings an important contribution to the seemingly never-ending controversies on the adequacy and formulations of thyroid hormone replacement therapy. Over the last few years, many professional organizations have tackled this question using the current and past literature, clinical trials, and mechanistic studies to derive evidence-based recommendations on the indication and proper therapeutic use of thyroid hormone and thyroid extracts (2-7). The overall theme of these guidelines is that levothyroxine (LT_4) alone is the preferred drug for the treatment of hypothyroidism, and that there is little evidence supporting the superiority (or the indication) of combination therapy or the use of thyroid hormone extracts. All the published guidelines also lament the paucity of well-conducted, adequately powered studies designed to characterize the effectiveness and superiority of one treatment modality versus the other. Layered on the objective scarcity of primary data, a vocal minority of patients, patients' advocates, and practitioners is convinced that by endorsing LT_4, the "chemical form" of thyroid hormone, the professional organizations are depriving patients of the opportunity of receiving what is described as "natural," "bioidentical," or "personalized" treatment. The fiery nature of online and written commentaries clearly demonstrates that (at least for some) the argument is far from settled. This scenario is reminiscent of the controversies that accompanied the introduction of new formulations of insulin, initially human recombinant, and eventually modified forms, leading to the discontinuation of the distribution of porcine and bovine "natural" insulin (8).

Hypothyroidism is a very common condition, particularly in the adult population: in 2014, LT_4 accounted for a total of 22,258,461 prescriptions, resulting in an astonishing cost of $969,060,446 (9). These figures indicate that LT_4 is the second (in prescriptions) and the 65th (in sales) drug in the U.S. market. Since 1997, after almost half a century since its introduction to the market, LT_4 manufacturers sought and gained U.S. Food and Drug Administration approval for their formulations (10). Moreover, one would assume that thyroid hormone extracts and compounded formulations underwent the same degree of scrutiny similar to LT_4, but the history of the development and marketing of these formulations, as clearly described by Dr. Hennessey (1), precedes the regulatory framework we as practitioners are used to.

Placing thyroid hormone replacement therapy within the proper historic perspective allows one to understand several apparent paradoxes. Simply put, at a time when, aside from the clinical observation, very little objective assessment was at the disposal of clinical investigators, the level of evidence necessary for including thyroid hormone extracts in the physicians' armamentarium was the at times anecdotal "self-evidence" of the clinical effect. Similarly, one should consider that accurate and precise measurement of thyroid hormone content was long considered an aspirational goal, and the measurement of protein-bound iodine has represented, until the introduction of the radioimmunoassay (11), the state of the art in estimating thyroid hormone content in serum and tissue extracts. Finally, it is important to consider that the governmental regulatory framework expected from new drugs simply did not exist when physicians began treating hypothyroid patients with thyroid extracts (Fig. 1). Thus, it should not come as a surprise that a century after the introduction of thyroid

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hormone replacement therapy, there are not properly powered controlled studies on the efficacy and effectiveness of various forms of thyroid hormone replacement therapy; there is relative latitude in the determination of the potency of the individual formulation, and a never-ending controversy on the optimal therapeutic target and indices of adequate thyroid hormone action still lingers.

On the other hand, Hennessey's narration (1) clearly indicates the struggle of researchers and physicians to develop a safe and predictable delivery of thyroid hormone therapy. The initial reports of morbidities and fatalities (which nowadays would be defined as "serious adverse events") (12) pointed to the risks associated with a small therapeutic index active ingredient (triiodothyronine) whose concentration varies between species and from batch to batch of raw material. As clinical and laboratory tools became more precise and reproducible (11), so did the expectations of a predictable therapeutic effect. So it is not a surprise that once LT_4 became widely available, by simply fulfilling a clinical need, it quickly surged to such a dominant role in the market.

For some constituencies across the spectrum of interested parties (patients and patients' advocates, practitioners, and entrepreneurial small-scale manufacturers), what was considered a clinical necessity (i.e., predictability and standardization of thyroid hormone therapy) has more recently become an unwanted restraint in therapeutic choice and optimization of care. Once again the historic perspective may help in framing this apparent paradox. The initial target for thyroid hormone replacement therapy were patients with profound hypothyroidism, and the diagnostic tools (initially protein-bound iodine, thyroid hormone assays, and first- and second-generation thyroid-stimulating hormone [TSH] assays) could only identify the most severe (and presumably the most symptomatic) cases of hypothyroidism. Hence, it is not a surprise that a "good enough" therapy would look like a miracle drug at that time, not dissimilarly from the first successes in insulin therapy (13). As the ability to detect the most subtle forms of thyroid dysfunction has improved, the prescription of thyroid hormone replacement has moved from severely symptomatic patients to individuals whose symptoms and signs are very difficult to pinpoint and are often vague and nonspecific. Nonetheless, the expectations are high, and both patients and practitioners feel the pressure toward an ever more difficult "therapy optimization." The renewed interest in the study of the peripheral conversion of thyroid hormone in the delivery of the hormonal message (14) has brought novel clinical data which support the notion that LT_4 alone may not be sufficient to provide

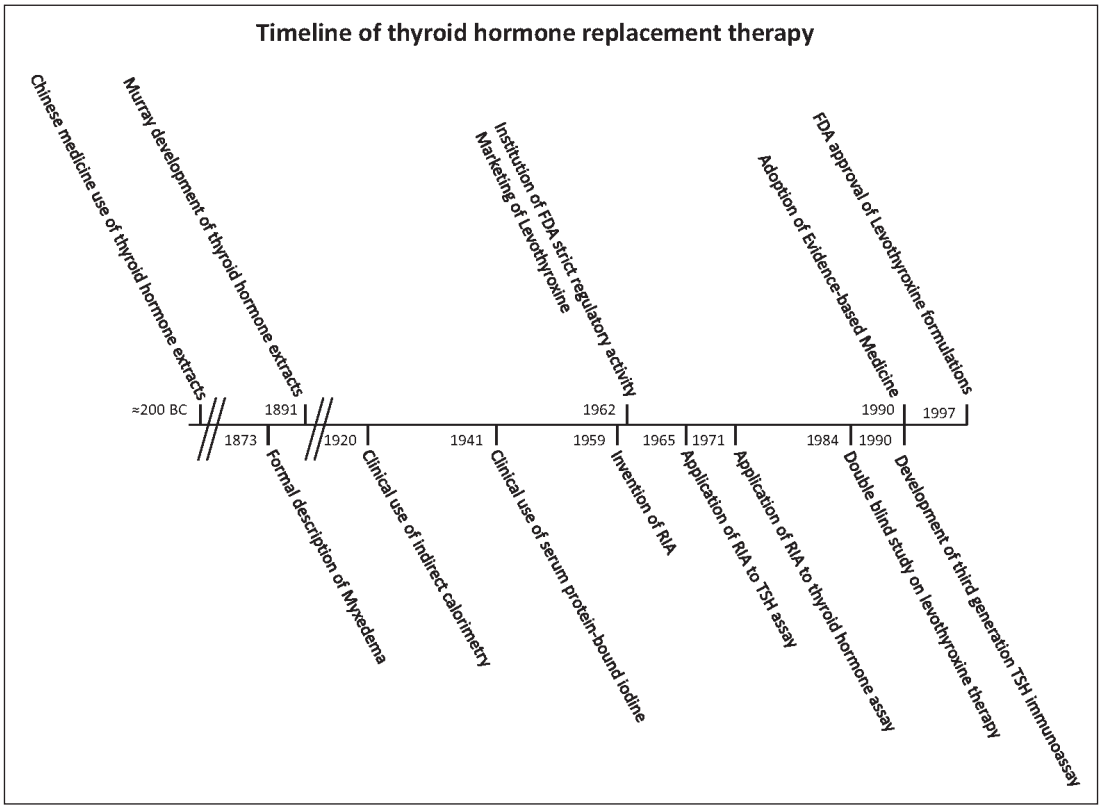

Fig. 1. Timeline of thyroid hormone replacement therapy (19) and regulatory framework (top) and significant clinical (20,21) and technological (22-25) developments (bottom). *FDA* = Food and Drug Administration; *RIA* = radioimmunoassay; *TSH* = thyroid-stimulating hormone.

"optimal" thyroid hormone replacement in all the tissue targets, or at least in some individual carriers of genetic variants of the deiodinase genes. There is, however, a disconnect between the clinical and translational research findings (often obtained in very well-defined controlled research contexts), the actual extent ("effect size") of the alternate treatment (in a comparison trial), and last but not least, the practicality and the potential untoward effects of such treatments. The decrease in weight and cholesterol achieved using pharmaco-equivalent (defined as the ability of equally inhibiting the thyrotroph) doses of liothyronine (LT_3) achieved in a closely controlled research environment on a thrice daily administration regimen (15) does not appear applicable in the day-to-day clinical practice. Indeed, it is worth noting that even in the most controlled conditions, the therapeutic target (a TSH >0.5<1.5 μIU/mL) was achieved after an average dose-finding period of almost 6 months. In practice, one could expect to have the patient over- or undertreated for the majority of time, hardly a therapeutic success! Similarly, a secondary analysis on a large parallel trial of LT_4/LT_3 combination versus conventional LT_4 therapy (16) demonstrated that carriers of the common Thr92Ala D2 polymorphism (17) have at baseline lower scores in some quality of life assessment instruments, which improve after treatment with LT_4/LT_3 combination. Aside from technical issues related to the study design and analysis, one outstanding question has not been addressed (yet): what does an *x* improvement in a research tool mean when translated in the day-to-day life of a patient? In other words, what is the real impact of it? Nonetheless, these studies have the merit of highlighting our current lack of knowledge and serve as a springboard to promote novel research aimed not only at demonstrating a significant difference in study parameters but also to show the effectiveness of the intervention in real-life scenarios. On the other hand, it is necessary to recognize that thyroid hormone extracts, albeit neither "physiologic" nor adequate from the pharmacokinetics standpoint, have been successfully used in the treatment of hypothyroidism (18).

Conversely, while the therapeutic use of thyroid hormone extracts may give pause, the use (and abuse) of thyroid hormones and extracts in formulations branded as nutritional supplements is simply terrifying. Dr. Hennessey's description of the lethal effects of these concoctions (1) has the value of placing these incidents the correct timeline: from unavoidable side effects of crude preparations to the result of unscrupulous entrepreneurs who thrive by promoting "natural," "bioidentical," and "personalized" forms of treatment completely outside any regulatory or quality control supervision, then market these supplements by capitalizing on the skepticism toward the "official, mainstream, big brother" medicine. Similarly, the lack of control in formulations produced in compounding pharmacies should prompt practitioners to question the risk to benefit ratio when it comes to counsel our patients about abandoning the current "good enough" status in favor of advantages that are very difficult to quantitate with the currently available clinical diagnostic tools.

In conclusion, the historic perspective of the development and use of thyroid hormone and thyroid extracts for the treatment of hypothyroidism is a valuable lens to look into and recognize the enormous progress made by the clinical and experimental thyroidology, as well the current gaps in knowledge. The next challenges will thus lie in the definition of instruments sensitive and at the same time clinically relevant, able to detect small but important differences, reconciling the gap between efficacy versus effectiveness trials. Another challenge resides in the characterization of the ideal LT_3/LT_4 ratio and the development and validation of a sustained release formulation to allow a once a day regimen. These are necessary milestones whose achievement is a precondition for the design and implementation of a comparison trial aimed at quantifying the differences, including the pharmacogenomics component, between conventional versus combination therapy or thyroid hormone extracts.

DISCLOSURE

The author has no multiplicity of interest to disclose.

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