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COMMENTARY

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Time to refresh thinking on the terminology and management of hypothyroidism?

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Replacement therapy with L-thyroxine is not universally successful at reversing all symptoms for people with hypothyroidism.[1] For such patients, current guidelines recommend looking for other co-morbidities including hypoadrenalism, celiac disease, anaemia, hypercalcaemia, sleep apnoea, renal failure and other conditions. If there are ongoing symptoms, recent focus has been on the possible utility of liothyronine. The timely review by Perros et al[1] argues about thinking beyond this narrow perspective to look at broadening potential treatments as well as expanding research ideas.

The reviewers (1) explain that somatic symptoms are likely to coexist with common conditions such as hypothyroidism. In the same way that people with depression or hypogonadism may benefit from a combination of pharmacological and psychological input, such as cognitive behavioural therapy, it is argued that some people with hypothyroidism may also benefit from such a combined approach. Limited access to clinical psychology in many areas should not limit our aspirations to offer such care and explore which forms of psychological input may help most. Intriguing early data is presented that reducing the "inflammatory" load by thyroidectomy or selenium may help adverse symptoms. Further research is required before these interventions, metformin[2] and other approaches to reduce the inflammatory load can be recommended. They also encourage us not to neglect the impact of treating depression, improving physical activity and managing obesity can have on well-being in people with hypothyroidism. The authors suggest that using liothyronine is ineffective, at least for the vast majority of people with hypothyroidism, as judged by the lack of benefit in meta-analyses of randomized controlled trials (RCT).

Although liothyronine may not resolve ongoing adverse symptoms in the majority of people with hypothyroidism, it may be premature to dismiss it altogether. Future RCTs may be better focussing on those with persistent adverse symptoms[3] rather than anyone with hypothyroidism. Also, the interaction between liothyronine use and genetic polymorphisms is intriguing although not well characterized.[4,5] It is noteworthy that the meta-analyses do not demonstrate the superiority of L-thyroxine over combined L-thyroxine and liothyronine, which throws the focus onto the cost and safety of liothyronine. The excessive cost of liothyronine in the UK is being investigated[6] but currently makes it difficult for healthcare providers to recommend liothyronine until there is strong evidence of its benefit. Safety data are as yet limited, but do not identify major concerns on human data.[7,8] The control of tissue liothyronine concentrations involving membrane receptor uptake, de-iodination, nuclear thyroid receptor binding and other nuclear protein binding is complex.[9] Pharmacological tools to manipulate these processes are currently lacking and it is not possible to fine-tune intracellular liothyronine concentrations, or its downstream intracellular effects.

We have previously reported that only 62% of patients on L-thyroxine have a serum TSH in the reference range[10] and others report similar data,[11] suggesting that current treatment goals with L-thyroxine alone are frequently not achieved. This is however cross-sectional data. We can report longitudinal data in our local cohort of 11,335 hypothyroid patients treated only with L-thyroxine. Over a mean of 12-year follow-up (range 1–25 years) with an average 1.25 TSH tests per year, only 1360 (12%) never had a serum TSH out with the reference range (unpublished data). If followed up for 15–25 years (mean 19 years), only 4% of 2710 patients always achieved

a serum TSH in the reference range. Does this reflect variable drug absorption impacted by foods and other interfering medications, variable drug delivery, variable concordance, variable metabolism and elimination of absorbed thyroxine, or some other issue affecting variable serum TSH concentrations? In reality, it may be all these factors, but it gives plenty of scope to explain and highlights the need to explore, some of the adverse symptoms experienced by patients on L-thyroxine.

TSH assays are not perfect,[12] as there is the potential for assay interference, and unexpected results should be interpreted in the context of previous and repeated tests. Despite this, TSH assays are the best measure adequacy of thyroid replacement that is currently available,[13] although there may be potential for better tests in the future.

Clinicians are starting L-thyroxine[10] at increasingly lower concentrations of serum TSH.[11] Despite guidelines not recommending L-thyroxine when people have subclinical hypothyroidism with serum TSH between 4 and 10 mU/L and normal free thyroid hormone concentrations, treatment is often started in an attempt to improve symptoms which were unlikely to be due to thyroid dysfunction. This can create unrealistic patient expectation and dissatisfaction when starting on a prolonged course of L-thyroxine. It is noteworthy that a third of patients previously established on L-thyroxine remain biochemically euthyroid when L-thyroxine is stopped.[13] This is three times more common if the original diagnosis was subclinical hypothyroidism compared with overt hypothyroidism.[14] When patients with troublesome symptoms have biochemistry results returned and the term subclinical disease is used, the question may be raised as to whether this really is "sub" clinical. The temptation can be to start L-thyroxine to see whether it helps some symptoms even though it has been shown that three or more symptoms of hypothyroidism are required to have any predictive power of distinguishing hypothyroidism from non-thyroidal illness.[15] Perhaps now is the time to abandon the term "subclinical hypothyroidism". In diabetes the term, "pre-diabetes" is used to identify patients who are at risk of developing diabetes but who do not have diabetes mellitus. A term such as "pre-thyroid" or "pre-hypothyroid" may be preferable. However, the term pre-hypothyroidism still telescopes the "hypothyroid" propensity of the condition. To avoid this issue, the term pre-thyroid could be used for what is currently called subclinical hypothyroidism and subclinical hyperthyroidism using a grading scheme similar but subtly different to that previously proposed.[16] People with a normal free T4 and free T3 could be categorized as pre-thyroid disease grade 1 (TSH 4–10 mU/L), grade 2 (TSH > 10mU/L), grade 3 (TSH 0.1–0.4 mU/L), grade 4 (TSH 0.03–0.1 mU/L) and even grade 5 (TSH < 0.03 mU/L). This approach could identify patients with "grade 1 pre-thyroid disease" who are at risk of thyroid disease but who do not yet have thyroid disease and will not benefit from pharmacological treatment, but who require ongoing monitoring, and thus creating more realistic expectations.

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REFERENCES

1. Perros P, Van der Feltz-Cornelis C, Papini E, Nagy EV, Weetman AP, Hegedus L. The enigma of persistent symptoms in hypothyroid patients treated with levothyroxine: a narrative review. *Clin Endocrinol*. 2021:94. https://doi.org/10.1111/cen.14473
2. Jia X, Zhai T, Zhang J. Metformin reduces autoimmune antibody levels in patients with Hashimoto's thyroiditis: a systematic review and meta-analysis. *Autoimmunityn*. 2020;53:353-361.
3. Jonklaas J, Bianco AC, Cappola AR, et al. Evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism: a consensus document. *Thyroid*. 2021;31:156-182.
4. Panicker V, Saravanan P, Vaidya B, et al. Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. *J Clin Endo Metab*. 2009;94:1623-1629.
5. Carlé A, Faber F, Steffensen R, Laurberg P, Nygaard B. Hypothyroid patients encoding combined MCT10 and DIO2 gene polymorphisms may prefer L-T3 + L-T4 combination treatment - data using a blind, randomized, clinical study. *Eur Thyroid J*. 2017;6:143-151.
6. Liothyronine tablets: Suspected excessive and unfair pricing. 2020. https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct. Last Accessed 31 March, 2021.
7. Leese GP, Soto-Pedre E, Donnelly L. Liothyronine use in a 17 year observational population-based study- the TEARS study. *Clin Endo*. 2016;85:918-925.
8. Planck T, Hedberg F, Calissendorff J, Nilsson A. Liothyronine use in hypothyroidism and its effects on cancer and mortality. *Thyroid*. 2021. https://doi.org/10.1089/thy.2020.0388. Online ahead of print.
9. Williams GR, Bassett JHD. Thyroid diseases and bone health. *J Endocrinol Invest*. 2018;41:99-109.
10. Flynn RV, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum Thyroid Stimulating Hormone Concentration and Morbidity from Cardiovascular Disease and Fractures in Patients on Long-term Thyroxine Therapy. *J Clin Endo and Met*. 2010;95:186-193.
11. Taylor PN, Iqbal A, Minassian C, et al. Falling threshold for treatment of borderline elevated thyrotropin levels-balancing benefits and risks: evidence from a large community-based study. *JAMA Intern Med*. 2014;174:32-39.
12. Favresse J, Burlacu M-C, Maiter D, Gruson D. Interferences with thyroid function immunoassays: clinical implications and detection algorithm. *Endocr Rev*. 2018;39:830-850.
13. Okosieme O, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. *Clin Endo*. 2016;84:799-808.
14. Burgos N, Toloza FJK, Singh Ospina NM, et al. Clinical outcomes after discontinuation of thyroid hormone replacement: a systematic review and meta-analysis. *Thyroid*. 2020. https://doi.org/10.1089/thy.2020.0679. Online ahead of print.
15. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160:526-534.
16. Wiersinga WM. Guidance in subclinical hyperthyroidism and subclinical hypothyroidism: are we making progress? *Eur Thyroid J*. 2015;4:143-148.

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