Levothyroxine absorption test: An underutilized tool

Delini Devi Ramadras, MD[1,2], Hanisah Abdul Hamid, MPATH[1], Julia Omar, MPATH[2]

[1]Chemical Pathology Unit, Pathology Department, Hospital Tengku Ampuan Rahimah, Klang, Selangor, [2]Chemical Pathology Department, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, Kelantan

SUMMARY

A subset of hypothyroid patients who are refractory to standard thyroid hormone replacement treatment is commonly encountered causing patients to be prescribed with high doses of levothyroxine. However, it remains a challenge to clinicians to distinguish nonadherence from malabsorption in patients with uncontrolled hypothyroidism despite the administration of high doses of levothyroxine. Here, we present a case of a 55-year-old woman with refractory hypothyroidism who was subjected to the levothyroxine absorption test (LT4AT).

INTRODUCTION

The levothyroxine absorption test (LT4AT) is typically performed by administering a single large oral dose of levothyroxine (LT4) with serial measurements of FT4. It is performed on patients with uncontrolled hypothyroidism despite the administration of high doses of oral LT4. This test is performed to effectively distinguish the cause of uncontrolled hypothyroidism due to poor compliance secondary to nonadherence or malabsorption of the drug.[1] In most patients, hypothyroidism is readily treated with oral LT4 replacement with doses ranging from approximately 0.8 - 2.1 µg/kg.[2] However, it becomes a challenge for clinicians involved in predicaments where patients have an inadequate response to a seemingly appropriate dose of levothyroxine (LT4) in the absence of known conditions or medications that impair LT4 absorption. This case report aims to distinguish nonadherence in a patient with refractory hypothyroidism despite the administration of high doses of levothyroxine by performing LT4AT and highlighting its importance in the diagnosis of LT4 pseudomalabsorption. The term pseudomalabsorption of levothyroxine is frequently used when important organic causes, concomitant medications, intrinsic gastrointestinal disorders, pharmacodynamics-modifying drugs have been ruled out.[3]

CASE REPORT

A 55-year-old female on daily intake of LT4 of 250 ug was classified by the treating physician as refractory hypothyroidism. She weighs 69 kg and LT4 dosage requirement is 1.6 µg/kg body weight. Her thyroid-stimulating hormone (TSH) remains high (>150 mu/L) despite increasing the LT4 dosage as shown in Figure 1. She claims to take the medication accordingly as instructed and took no other medications that were potential to alter the absorption of LT4. All biochemical tests including haemoglobin were within normal range. She was referred to the pharmacist for evaluation of compliance. The patient expressed her frustration about the treatment not being any help to her condition and subsequently agreed to undergo further testing. She was subjected to the LT4AT after having fasted for 8 hours and omitting her daily LT4 dose for the day. A protocol by Lima et al.[4] was used with a slight change in the time of blood collection measurement of TSH and FT4. Blood for serum FT4 at 0, 60, 120, 180, 240, 300, 360 minutes and serum TSH at 0 and 360 minutes were taken after administration of 1000 µg of LT4 orally. The results of her TSH and FT4 were as in Figure 2.

Her results showed an increase in FT4 initially for the first 180 minutes and a plateau till the end of 360 minutes. The FT4 increment was 2.7 times higher than the baseline. In this patient the FT4 increment from baseline (5.0pmol/L) at 3 hour is 13.7 pmol/L (1.06ng/dL). The TSH level fell accordingly and was compatible with normal absorption. Thus, inadequate levothyroxine absorption was therefore excluded. This finding excluded her from the need of a potentially exhaustive search for an organic underlying cause.

DISCUSSION

Hypothyroidism is characterized by low levels of thyroid hormones in the blood. It is common in women with a female-to-male ratio of 6:1.[5] Primary hypothyroidism occurs when there is a destruction of the thyroid gland due to autoimmunity which is the commonest cause, resulting in low thyroid hormones. It accounts for more than 90% of cases of hypothyroidism and effective hormone replacement can be achieved in most patients clinically with a daily intake of LT4. The ingested LT4 absorption occurs primarily in the duodenum and jejunum in approximately 62% to 81% within 3 hours of oral ingestion. Optimal dissolution of the drug particles and proper ionization of thyroxine requires low gastric pH[6]. LT4 undergoes hepatic metabolism and is partially deconjugated and resorbed in the intestinal tract.

Patients with clinical and biochemically uncontrolled thyroid function, even in the use of adequate doses of oral LT4, represent a challenge in clinical practice. When compared to other minimally invasive test available to rule out malabsorption such as esophagogastroduodenoscopy (OGDS) and colonoscopy, LT4AT is definitely cost effective and widely available in most laboratories. The LT4AT is an important test to consider for distinguishing between nonadherence and true intestinal pseudo malabsorption (after excluding gastrointestinal and liver diseases,

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Corresponding Author: Delini Devi Ramadras
Email: delinidevi@gmail.com

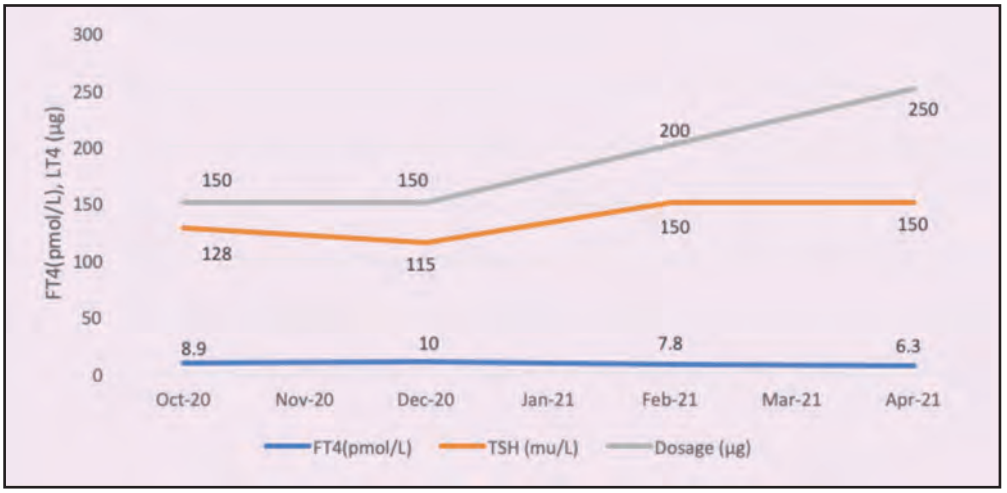

Fig. 1: Thyroid function trend prior to LT4AT

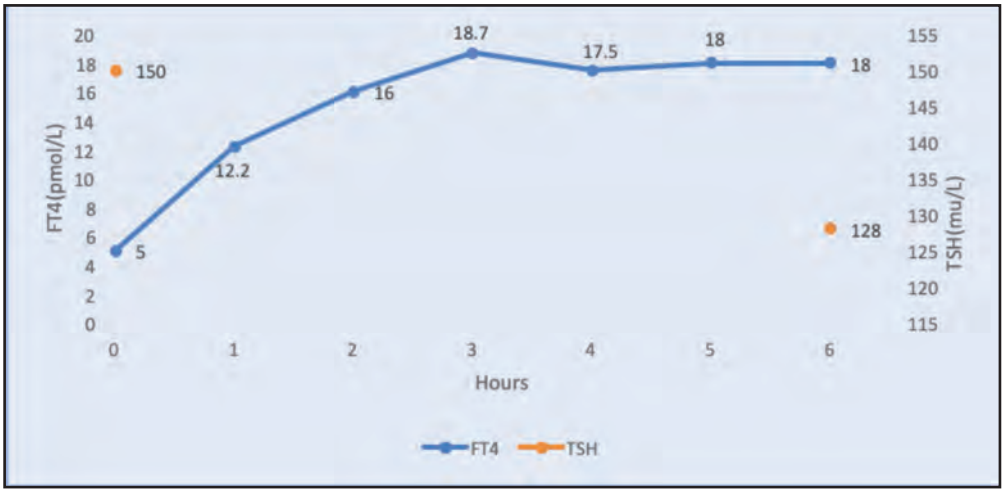

Fig. 2: Levothyroxine absorption test curve

medication and dietary interference), the latter of which is very rare. If nonadherence is suspected, the options to confirm the possibilities are limited especially when patients do not report such behaviour.

There is no gold-standard method for the LT4AT with various protocols advocated in the literature. In most case reports, LT4AT was conducted under the supervision of LT4 ingestion with a dose of 1000 µg orally. Observation of the patient for at least 60 minutes after ingestion is important to evaluate if the patient develops any symptoms and to ensure compliance. In patients with hypothyroidism, the FT4 usually increases 1 hour after LT4 intake and achieves a peak at 2 hours.[7] Several small studies reported good absorption of levothyroxine in such patients; however, there was no suggestion for any cut-off for LT4 increment to rule out pseudomalabsorption.[7] For the interpretation of LT4AT, many authors suggest that an increment of at least 2.5 times from the baseline of FT4 is suggestive of pseudomalabsorption.[6] According to Ghosh et al., the cut off of free T4 increment at 3 hours from baseline above 0.40 ng/dL (5.14 pmol/L) had a sensitivity of 97% and specificity of 80% (AUC 0.904, $p < 0.001$) to exclude true malabsorption.[8]

Another way of interpreting LT4AT testing suggested by some authors was by calculating the LT4AT using the volume of distribution (Vd) to estimate the amount of drug absorbed. Vd (liters) is measured as Vd=0.442 x body mass index (BMI). Based on this, the percentage of drug absorption can be estimated by the formula of LT4 absorbed (%) = peak TT4 (µg/ dL) x Vd (dL)/ administered dose of LT4 x 100. A normal absorption is taken as ≥60%.[9]

Based on Sun Ge et.al study, FT4 and TT4 correlated highly, in patients who were severely hypothyroid. FT4 may be used as a qualitative assessment of suspected malabsorption using an oral LT4 absorption test for the evaluation and management of hypothyroidism dosage of FT4 in association with TSH is widely recommended.[10]

In this patient, adequate absorption of LT4 was demonstrated with a subsequent prominent spike in FT4 levels and

concomitant suppression of TSH suggested of pseudomalabsorption. She was counselled on how current symptoms could be attributed to poor disease control due to irregular administration of vital medications. She was advised on regular administration of LT4 for better symptom control which she was agreeable as she realised that her adherence made improvement to her thyroid function test. Further plans were to monitor and further analyse her for a psychiatric condition if non-compliance still exist.

CONCLUSION

For patients with suspected 'pseudomalabsorption' of levothyroxine, the thyroxine absorption test may aid clinicians in establishing poor compliance with objectivity and confidence. The lack of uniformity in practice or interpretation of this test may have led to it being underutilized. We report a case of pseudo malabsorption where a rapid 6-hour thyroxine absorption test allowed us to objectively prove adequate LT4 absorption, leading to a reduction in LT4 dosing, without the need for potentially more invasive testing. Concurrently, this would establish a clearer view and awareness to the patient regarding the need of adherence for finer disease control. A standard protocol of LT4AT is needed with a clear objective and selection of patients to help in the management of hypothyroid patients.

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