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Levothyroxine absorption and difficult management of hypothyroid patients in the intensive care unit: two case reports and a literature review

Interferências na absorção de levotiroxina e dificuldades no manuseio de pacientes com hipotireoidismo na unidade de terapia intensiva: relato de dois casos e revisão de literatura

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ABSTRACT

Levothyroxine absorption in hypothyroid patients can be influenced by several factors, particularly medications and concomitant food administration. This is especially evident in intensive care unit patients, where a continual enteral diet and the administration of multiple medications changes its absorption. Changes or adaptations in the hypothalamic-pituitary-thyroid axis, in conjunction with clinical abnormalities possibly related to undertreatment of hypothyroidism, render levothyroxine replacement therapy very challenging. Here, we report two inten-

sive care hypothyroidism patients and their respective levothyroxine replacement management issues, focusing on a number of controversial issues, such as the optimal replacement dose, how fast the levothyroxine doses should be increased, triiodothyronine requirements, the interference of an enteral diet with absorption, and finally, the possible consequences of undertreated hypothyroidism and levothyroxine replacement monitoring useful clinical/laboratory parameters.

Keywords: Absorption; Levothyroxine/pharmacokinetics; Hypothyroidism; Critical care; Case reports

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INTRODUCTION

Levothyroxine (LT₄) replacement is a widely accepted hypothyroidism therapy. It has recently been studied both alone or combined with triiodothyronine (T₃) in the outpatient setting.^(1,2) Initial LT₄ replacement with gradual dose escalation is classically recommended for outpatients. On the opposite end, myxedematous coma patients require more aggressive replacement⁽³⁾, both because the condition is life-threatening and because of likely difficult intestinal absorption. Between these two extremes are critically ill hypothyroidism patients (without myxedematous coma) who are in an intensive care unit for non-hypothyroidism causes. Management of these patients is poorly studied, but is an important clinical practice challenge. Appropriate hypothyroidism therapy may be determinant for intensive care patients' recovery, particularly with regard to hemodynamic conditions and mechanical ventilation-dependent respiratory failure. Another group of patients are those without a diagnosis of hypothyroidism who may have critical illness adaptive changes that resemble hypothyroidism (euthyroid sick syndrome). LT₄-compensated hypothyroidism patients should be managed carefully, as they rely on fixed LT₄ oral doses and may eventually not be able to "self-adjust".

Two cases of hospital-acquired pneumonia and respiratory failure in hypothyroidism patients are presented here, together with our choices for LT₄ and eventually triiodothyronine (T₃) replacement. A review of the factors interfering with drugs absorption in critically ill patients is presented, including a discussion on how critically ill patients' adaptive mechanisms can influence their replacement dose management.

CASE REPORT

Case 1

J.M.S., an 80-year-old man, was seen at the outpatient clinic in August 2006 with decompensated hypothyroidism due to disordered therapy. He was diagnosed with primary hypothyroidism in 1994. He had been managed at the outpatient clinic with levothyroxine 100 µg/day (1.1 µg/kg/day), but discontinued the therapy for 70 days. The patient reported drowsiness, asthenia, constipation and myalgias and had drawled speech. His physical examination showed discoloration (+/++++), eupnoea, periorbital edema, bradycardia, a blood pressure of 150/70 mmHg, a weight 90 kg and a height 1.75 m. Hypophonic heart sounds were heard and lower limb edema was present; no other relevant physical findings were present. The patient was admitted to the endocrinology ward and started on LT₄ replacement for the associated comorbidities.

He was taking 10 mg/day glibenclamide for diabetes mellitus and 100 mg/day acetylsalicylic acid. He reported untreated hypertension and pulmonary emphysema. The patient was a long-term smoker with a 50 pack-year history.

An admission laboratory panel showed decompensated hypothyroidism, with a thyroid stimulant hormone (TSH) of 88.02 µU/mL (reference value: 0.4-4.5), a free T₄ (FT₄) of 0.08 ng/dL (reference value 0.8-1.9), anemia of chronic illness with a hematocrit (Htc) of 33% and a hemoglobin (Hgb) of 11 g/dL, a white blood-cell count that was negative for infection, a blood glucose of 181 mg/dL, and a creatinine of 1.7 mg/dL. No other laboratory values were remarkable (Table 1).

LT₄ replacement was started at 12.5 µg/day, with progressive dose increments for 15 days up to 62.5 µg/day. On the 16th hospital day, after he was clinically compensated, the patient experienced hemoptysis and had crackling at the right pulmonary base, so he was started on oral antibiotics. Five days later he showed no improvement and had dyspnea at rest, fever peaks,

Table 1 – Case 1 patient laboratory data

	Admission day	Hemodynamic decompensation day
Hematocrit	33%	25.1%
WBC	6,300	14,300
Rods	2%	17%
Blood glucose	181 mg/dl	201 mg/dl
BUN	55 mg/dl	65 mg/dl
Creatinine	1.7 mg/dl	2.1 mg/dl

WBC – white blood cell count; BUN – blood urea nitrogen.

diffuse crackles, a white blood cell count of 14.3 thousand/mm³ with a left shift (bands 17), and his Na⁺ was 131 mMol/L, K⁺ 5.5 was mMol/L and creatinine was 2.1 mg/dL (Table 1). The chest X-ray showed diffuse bilateral infiltrates. The patient progressed to ventilator-support-requiring respiratory failure and also required hemodynamic and enteral nutritional support. The LT₄ replacement dose was increased to 200 µg/day (2.2 µg/kg/day) via enteral administration, and corticoid therapy was started (hydrocortisone 200 mg/day) along with antibiotics and an intravenous proton-pump inhibitor (omeprazole).

Three days later, he had a clinical improvement while still on respiratory support; the sedation was reduced, and the LT₄ replacement was increased to 300 µg/day (3.3 µg/kg/day). After four days on high-dose LT₄ his hormone levels were FT₄ 0.96 ng/dL, and TSH 2.07 ng/dL (Table 2). Next, he underwent daily sedation withdrawal as proposed by Schweickert *et al.*,⁽⁴⁾ and was ready to wake in less than 30 minutes, assuring us that he had no hypothyroidism-related consciousness level issue.

Table 2 – Hormone dosages

Laboratory	Admission	7 days	LT ₄ 300	LT ₄ 300
progression	day – LT ₄	after LT ₄	µg/day	µg/day for
	started	escalation to	for 7 days	20 days
		200 µg/day)		
TSH	88.02	2.07		0.1
FT ₄	0.08	0.96	1.24	1.38

TSH – thyroid-stimulating hormone; LT₄- levothyroxine; FT₄ - free T₄.

His condition remained critical during the entire stay in spite of the laboratory hormone improvements. His last laboratory levels after 20 days on LT₄ 300 µg/day were FT₄ 1.38 ng/dL and TSH 0.10 ng/dL (Table 2). The patient progressed to septic shock with a pulmonary focus and eventually died 30 days after his admission.

Case 2

E.F.W., a 76-year-old female, had a height of 1.78 m and a weight of 90 kg and had been diabetic for 35 years, with microvascular complications including sensitive motor neuropathy, mild gastroparesis, and nonproliferative retinopathy. She had compensated hypothyroidism treated at the outpatient clinic and had been taking 125 µcg LT₄ (1.38 µcg/kg). Her hypothyroidism resulted from a surgery on a suspect thyroid nodule (histology confirmed that it was a benign follicular adenoma). Until March 2008, she was taking 16 units of insulin glargine once daily, with appropriate blood glucose control. She was also taking 80 mg/day valsartan, 20 mg/day pantoprazole, and 10 mg pre-prandial bromopride during post-meal vomiting phases.

One year earlier the patient sustained a right femoral neck fracture after a fall. Her postoperative antibiotic therapy was maintained for 21 days due to mild wound dehiscence. She completed her ciprofloxacin course as an outpatient after she was discharged from the hospital. Two months later she had a symptomatic *Klebsiella* urinary tract infection (extended-spectrum β-lactamase-producing – ESBL) and underwent ambulatory intra-muscular ertapenem therapy.

In April 2008, she was admitted for diverticulitis, which progressed to sepsis, but was discharged 10 days later after meropenem antibiotic therapy. Fifteen days later, she was unusually drowsy and had fever and hypotension; she was admitted to the hospital with a pneumonia diagnosis and progressed to septic shock. After the infection was brought under control, she could not be weaned from mechanical ventilation (mainly due to a recurrent 600-800 mL pleural effusion in each hemi-thorax). The pleural effusion was confirmed to be a transudate in two evaluations. She was continued on an enteral diet, and she was already taking 200 µg (2.2 µg/kg) LT₄, supporting the hypothesis that her hypothyroidism could be contributing to the pleural effusions. New laboratory evaluations showed a TSH of 12.0 µU/mL (reference 0.4-4.5) and an FT₄ of 0.7 ng/dL (reference 0.8-1.9). At this point, she had not received corticoids, as she had shown an appropriate response to vasopressors (noradrenalin), which were required for only 5 days. Thus, 20 µg /day T₃ was added to her T₄ therapy. Two Wayne catheters were inserted to drain both sides of the chest, retrieving about 1,000 mL every three days. The drainage

frequency and volume were progressively reduced until the catheters were draining 300-400 mL/week, at which time the patient was finally weaned from mechanical ventilation and discharged from the intensive care unit (ICU).

DISCUSSION

Sodium levothyroxine is commonly prescribed for physiological hypothyroidism replacement. The typical ambulatory replacement dose is 1.6 to 1.8 µg/kg/day;⁽⁵⁾ this translates to about 75 to 112 µg/day for females and 125 to 200 µg/day for males. Some patients may require higher or lower doses due to their individual absorption characteristics or other associated factors that can change their LT₄ needs, such as gastrointestinal diseases or the use of certain dietary supplements and drugs. Many thyroid hormone absorption trials have been conducted since 1960. Hormone absorption analysis methods have been developed to allow for evaluation of LT₄ bioavailability changes. Hays⁽⁶⁾ developed a compartment model based on gastrointestinal transport parameters, and LT₄ absorption was identified at the duodenum, jejunum and ileum, but mainly in the two latter sites, where 80% of an oral dose is absorbed. In the first few hours following oral intake, LT₄ is distributed mainly to the vessels and splanchnic organs before circulating to peripheral tissues, peaking within 2 to 4 hours.⁽⁷⁾ Therefore, the total serum T₄ increase should be proportional to the T₄ absorbed at several different times during the first six hours after intake.

Therefore, several issues need to be considered for T₄ absorption in critically ill patients, such as intestinal edema, hypoalbuminemia, continued enteral diet, and hypothalamic-pituitary-thyroid (HPT) axis adaptive changes. These may lead to additional LT₄ replacement management challenges both for hypothyroidism patients undiagnosed before the critical illness and for previously diagnosed hypothyroidism patients. This is true both for decompensated patients in the outpatient clinic, as in case one, and those considered compensated, as in case two.

HPT axis adaptive changes and their practical relationship with hypothyroidism patients will be discussed below, as well as common ICU drugs and dietary interference with T₄ absorption and bioavailability, particularly in critically ill patients.

Effects of gastrointestinal diseases on levothyroxine absorption

T₄ is mainly absorbed at the jejunum and upper ileum, and critically ill hypothyroidism patients may have a number of diseases at these sites. Celiac disease, pancreatic insufficiency, short bowel syndrome, inflammatory bowel disease and other conditions (including those affecting normal stomach acid secretion such as chronic atrophic gastritis and *Helicobacter pylori* infection) all can cause reduced LT₄ absorption. This is often evidenced by increased TSH while taking an LT₄ dose that would otherwise keep TSH normal. Celiac disease antibody measurements were proposed to be useful for patients requiring FT₄ doses $\geq 2 \mu\text{g}/\text{kg}/\text{day}$,⁽⁸⁾ as reported by Silva and Souza on an untreated celiac disease patient requiring a dose greater than $6 \mu\text{g}/\text{kg}/\text{day}$.⁽⁹⁾ However, no recommendations are available for replacement doses in critically ill patients, mainly due to the lack of laboratory parameters for dosage decision making.

Effects of food on LT₄ absorption

The interference of food with LT₄ absorption was shown by Benvenga *et al.*⁽¹⁰⁾ based on absorption curves and serum T₄ level changes. Coffee delayed absorption by at least one hour after LT₄ intake, resulting in TSH level normalization. However, additional evaluations are required to support the recommendation that LT₄ should be taken with an empty stomach one hour before a meal. Some food components, such as fibers and soy beans, may reduce LT₄ bioavailability.^(11,12) Even when LT₄ is given alone or parenterally, dietary fibers may interact with T₄ during its intestinal recycling in the T₄ enterohepatic cycle. T₄ clearance may also be increased independently of LT₄ and dietary fiber intake. Thus, in outpatients, TSH concentration monitoring is recommended in patients taking LT₄ who change their diets to include increased fibers and/or soy beans.^(11,12) In the continued enteral diets of critically ill patients, some drug absorption is estimated to be reduced by about 50% due to the diet infusion. Associated hypothyroidism may be an additional factor seen in conjunction with other changes normally seen in critically ill patients (such as fluid retention, renal failure, bowel edema, and vasoactive amines). However, no data on levothyroxine use in this group of patients is currently available. Thus, a logical, but also

speculative, suggestion would be to double the full dose recommended for outpatient clinic therapy to about 3 mcg/kg/day. In both cases here, the replacement was clearly above outpatient levels ($3.3 \mu\text{g}/\text{kg}$ for case 1 and $2.2 \mu\text{g}/\text{kg}$ for case 2), and in case 2, this was not enough to stabilize her ICU TSH levels, even with additional T₃.

Effects of drugs on thyroid hormones levels

Many drugs have been reported to affect LT₄ absorption, including ferrous sulfate, aluminum hydroxide, calcium carbonate, cholestyramine, sucralfate, and more recently, proton pump inhibitors, which in addition to affecting absorption may increase clearance.^(8,13) Among the mentioned drugs, only the proton pump inhibitor omeprazole was taken by both patients. Patients should be instructed to take LT₄ at least 3 hours after taking any of these drugs.⁽⁷⁾ Overall, the required LT₄ increase is less than twice the usual replacement dose.

In ICU patients, two drugs frequently reported to change the thyroid axis are glucocorticoids and sympathicomimetic amines (dopamine). Acute glucocorticoid doses inhibit the pulse TRH release, which reduces TSH levels and the T₃/T₄ ratio and concomitantly increases the rT₃ (reverse T₃)/T₄ ratio, suggesting that glucocorticoids increase Type 3 deiodinase activity.⁽¹⁴⁾ These changes are seen both in normal and hyperthyroidism patients, including LT₄-taking hypothyroidism patients. Dopamine inhibits TSH release, also resulting in reduced T₄ and T₃ levels.⁽¹⁵⁾ The case 1 patient was given corticoids at recommended dosage levels for sepsis,⁽¹⁶⁾ which may have contributed in part to the relatively fast TSH level reduction in the setting of normal FT₄ levels. The case 2 patient was given no corticoids but relatively short-term treatment with norepinephrine; however, given her critical status, hormone laboratory levels showed insufficient thyroid hormone replacement.

Thyroid axis changes and hormone metabolism

Generally, the hypothalamic-pineal axis is altered in intensive care unit patients. Frequently, hypophyseal hormone release is reduced, possibly from endogenous causes (due to the lack of hypothalamic input) or by drug administration (such as dopamine and glucocorticoids, as described above). In the thyroid axis, pulse TSH release is reduced, supposedly due to thyrotropin releasing

hormone (TRH) reduction, which is peripherally evidenced by low T3 and T4 levels and increased reverse triiodothyronine (rT3) levels. These changes, collectively called euthyroid sick syndrome, progressively worsen with the patients' clinical status, and can be classified into three stages:

1. Stage 1: reduced circulating T3 of up to 50%; modest rT3 increase; no serum FT4, TT4 (total T4) or TSH changes.

2. Stage 2: significantly reduced T4 clearance still maintaining pulse TSH release, leading to a modest FT4 increase; more serum T3 reductions and rT3 increases.

3. Stage 3: changes are accompanied by a lack of pulse TSH release and a drop in T4 and T3 levels. The patients are severely ill, and the changes may be seen as a severe disease pre-agonic phase, given the high mortality rates in these patients.

In compensated primary hypothyroidism patients with LT4 replacement who are hospitalized for non-thyroidal acute disease, some natural T3, T4, rT3 and TSH changes have been observed. As shown by Wadwekar and Kabadi,⁽¹⁷⁾ T3 and T4 levels drop to a trough level and an rT3 increase is seen on the 3rd hospital day; TSH is initially reduced, but increases by the 7th day before normalizing, probably secondary to transient thyroidal hormone metabolism changes. Additionally, recovery from critical illness is preceded by a circulating TSH level increase.⁽¹⁸⁾ In the case 2 patient, TSH levels were increased during the critical illness course, and remained high even during her recovery phase, rendering it difficult to discriminate the above-described phases.

Other highly relevant changes are those critical illness peripheral thyroid hormone metabolism changes that occur during the acute phase in addition to other thyroid axis changes. Type 1 deiodinase (D1), considered the main circulating T3 source, has its activity markedly reduced during critical illnesses compared to healthy subjects; however, this is a reversible reduction and is restored after TRH infusion, with T4 and T3 level normalization.⁽¹⁸⁾ Based on this, we chose to aggressively increase the LT4 doses, without fearing any heart or coronary disease deterioration, as the patient was already on sympathomimetic amines. Liver T4 capture is also reduced and is an additional factor causing reduced T3 production in these patients. Other peripheral changes include increased sulfated T4

(inactive), reduced thyroid hormone binding protein concentrations, and reduced nuclear receptor binding. In contrast to acute phase changes, chronic phase changes are unlikely to represent an adaptive response.⁽¹⁹⁾ During this phase, thyroid hormone levels are inversely correlated with hypercatabolic chemical markers (urea production and bone degradation), which may be reduced when the hormones are restored to physiological levels by continuous TRH infusion in combination with growth hormone (GH) secretagogues.^(19,20) So far, T4 administration has failed to show clinical benefit for these patients, perhaps due to the T4 to T3 conversion impairment.⁽¹⁸⁾ However, T3 replacement doses after congenital heart defect corrections have been associated with improved postoperative heart function.⁽¹⁸⁾ So far, however, there is no favorable evidence for treatment of the low T3 levels that are typical of prolonged chronic illness.⁽²¹⁾

Replacement management in critically ill patients

As mentioned above, the consequences of untreated hypothyroidism are only considered in intensive care units for suspected myxedematous coma, where aggressive hypothyroidism therapy (administered intravenously if possible) is required. Considering critically ill adaptive changes, it is frequently difficult to evaluate how much therapy is really needed; still, some clinical features may suggest hypothyroidism. Of note, consciousness level changes, difficulty with weaning from the ventilator (regardless of associated pleural effusion), gastrointestinal motility changes and hyponatremia may all have a contribution from untreated/undertreated hypothyroidism. In previously compensated patients, a critical illness may not require any levothyroxine dose adjustment; however, this must be based on individual experiences and may not correspond to actual thyroid hormone adjustment needs. Given the lack of any consistent literature evidence on non-myxedematous coma hypothyroidism patients' thyroid hormone management, the cases presented here exemplify how LT4 (and eventually T3) are usually replaced in our clinic (Table 3). The main issue is related to the phase when the changes are no longer protective and thus start impairing patient recovery. The length of intensive care unit stay is clearly increasing and will lead previously short and transient issues to become prolonged and recurrent ones.

Table 3 – Thyroid hormone replacement in hypothyroidism patients in three different clinical settings

Hormone replacement	Outpatient	ICU	Myxedematous coma
Intravenous LT4	-----	200 µg*	300-500 µg/day
Oral LT4	1.6 – 1.8 µg/kg	3 µg/kg	4 µg/kg
↑ dose	25 µg/ 2-4 weeks	↑ 50-100 µg	Full dose
Oral T3	?	?	?

*As used in our service; ICU – intensive care unit; LT4- levothyroxine; T3 – triiodothyronine; ? - unknown.

CLOSING REMARKS

The proposed LT4 doses for both cases' patients were about two-fold the usual replacement dose: 300 µg/day (3.3 µg/kg/day) for case 1 and 200 µg (2.2 µg/kg/day) plus T3 for case 2. This approach considered likely hormone absorption impairments such as proton-pump inhibitor use, gastric atonia and bowel mucosal edema, a continued enteral diet, and, in case 2, the difficulty of handling pleural effusions with contributing hypothyroidism. Withholding the diet one hour before and after LT4 dosing is one way of attempting to optimize absorption, but in critically ill patients this is still an unproven treatment. Similarly, questions regarding the interference of some enteral diet components with LT4 absorption and clearance still need to be answered. Hormone dose escalation is not required to be as slow as in outpatients, as deiodinase increase (the much-feared cardiac effect after "excessive" replacement) is clearly reduced. Additionally, the critically ill patient is already exposed to many myocardial stressful factors, such as the trauma metabolic response and the use of sympathicomimetic amines. As critically ill patients' adaptive changes may provide protein catabolism prevention (especially during the acute phase), the physician must decide whether T4 and T3 replacement is appropriate, particularly in hypothyroidism patients, as this is known to impair critically ill patient management with effects including slowed awakening from sedation and pleural effusions interfering with mechanical ventilation weaning. The schedule we used was based on objective LT4 absorption data, but was still only a guess at the critically ill hypothyroidism patients' actual LT4 (and eventually T3)

replacement needs. The patient's thyroid phase should also be studied, as replacements similar to physiological pulses have clearly been shown to be positive in studies on critically ill patient anabolic strategies. We suggest that special attention should be given to awakening after sedation withdrawal as a parameter for replacement appropriateness, and we suggest that free T4 levels should be monitored, given the well-known ICU influences on TSH levels.

RESUMO

Inúmeros fatores podem influenciar a absorção da levotiroxina nos pacientes hipotireoideos, especialmente medicações e administração concomitante com alimentos. Nos pacientes internados em unidade de terapia intensiva, estes fatores são mais evidentes, principalmente em função da dieta enteral contínua além de diversas medicações que podem interferir na sua absorção. Alterações adaptativas no eixo hipotálamo-hipófise-tireóide e alterações clínicas comumente presentes em pacientes críticos que podem ter contribuição de um hipotireoidismo não tratado se associam tornando ainda mais difícil o manuseio da reposição de levotiroxina. Relatamos dois casos de pacientes com hipotireoidismo internados em unidade de terapia intensiva, com suas respectivas abordagens para reposição de levotiroxina, levantando questões controversas como: qual a dose ideal de reposição, velocidade no incremento das doses, necessidade de associação com triiodotironina, interferência da dieta enteral na absorção, e finalmente as possíveis conseqüências de um hipotireoidismo não tratado e as formas clínicas e laboratoriais para monitorizar as doses hormonais administradas.

Descritores: Absorção; Levotiroxina/farmacocinética; Hipotireoidismo; Cuidados críticos; Relatos de casos

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