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Deprescribing in Patients of Hypothyroidism Results in Better Health Outcome: A Case Series

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ABSTRACT

Appropriate levothyroxine (LT4) dosing is essential in hypothyroid patients to maintain biochemical and clinical euthyroidism, but achieving appropriate plasma concentration of LT4 can be complicated by numerous disease states, foods, supplements, and commonly prescribed medications such as calcium supplements, pantoprazole etc. that potentially interfere with intestinal LT4 absorption. About one-third of treated patients are not receiving adequate treatment, leading to decreased quality of life, increased morbidity, and even increased mortality. Hypothyroid patients treated with LT4 must be careful to avoid concomitant ingestion of such medicines or optimal gap must be ensured between ingestions to prevent drug-drug interactions and reduce absorption of LT4. We describe two such real life cases managed in our clinical pharmacology consultation facility to highlight the importance of systematically evaluating the drug-drug interactions of levothyroxine with commonly used concomitant medications and how deprescribing of the same can result in attainment of optimum thyroid replacement with lesser doses of LT4 with better patient outcome.

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Introduction

Hypothyroidism is very common worldwide, diagnosed in up to 5% of the population with a peak incidence between age of 30 and 50 years (8–9 times more common in women than in men) , while another 5% of the population remain undiagnosed (1-3). Levothyroxine (LT4) is the mainstay of treatment for hypothyroidism, and is available as tablets and soft-gel caps, intravenously, and, more recently, in liquid formulations with the aim of improving adherence (4-6). The levothyroxine dose is titrated until TSH levels are normalized at between 0.4 and 4.0 mIU/L (7,8). As levothyroxine is classified as a narrow therapeutic index medication (small differences in dose or blood concentration may lead to therapeutic failure or adverse drug reactions), the American Association of Clinical Endocrinologists, American Thyroid Association (ATA) and the Endocrine Society recommended the consistent use of a single preparation of brand-name levothyroxine over generic preparations, which can vary in potency (9,10). In subclinical hypothyroidism, doses around 50–75 µg may be sufficient for normalizing the serum TSH. Once initial treatment has begun, monitoring of serum TSH and serum fT4 should be performed every 4 to 6 weeks until TSH is reduced to normal limits and the patient is in a euthyroid state. Thereafter, patients with stable normal serum TSH levels should be monitored every 12 months (11). In most cases, disease control is easily accomplished, with full recovery upon adequate replacement of thyroid hormones. Over a period of years, levothyroxine replacement dose may require adjustment as the disease progresses or if the patient develops other conditions that affect thyroid hormone metabolism. Doses can be adjusted according to patient symptoms and the dose at which TSH normalizes (12). More than a third of patients remain inadequately treated despite levothyroxine therapy, with evidently elevated TSH levels and/or persistent symptoms, leading to decreased

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quality of life, increased number of sick leave days, and even increased mortality (13-17). Achieving appropriate doses of LT4 can be complicated by concomitant disease states, foods, supplements, and medications like calcium carbonate, aluminum- containing antacids, sucralfate, iron supplements, cholestyramine, sevelamer, and, possibly, ciprofloxacin, raloxifene, pantoprazole and orlistat that potentially interfere with intestinal LT4 absorption (18). The magnitude of virtually all drug interactions tends to vary substantially from one individual to another that reduce levothyroxine serum concentrations, leading to a compensatory increase in TSH level and the need to increase levothyroxine dosage. Hypothyroid patients treated with LT4 must be careful to avoid concomitant ingestion of such substances or take them with sufficient gap between ingestions. We describe two such real life cases managed in our clinical pharmacology consultation facility to highlight the fact that these interacting drugs may have a clinically important effect on levothyroxine serum concentrations and how systematic evaluation of the drug-drug interactions of levothyroxine with commonly used concomitant medications and necessary deprescribing can result in optimum thyroid replacement with better patient outcome.

Case presentation 1

On 22 Mar 2022, AT, 32-year-old female, presented with complaints of extreme fatigue and episodes of feeling low since last two weeks. She gave history of unusual weight gain (approx. 10 kg in last three months). She was four months post-partum with her first pregnancy. She had an uneventful pregnancy with full term normal delivery. She was taking calcium carbonate tablet (1000 mg once a day in morning) since last 3 months. On physical examination, body mass index (BMI) was 30.6 kg/m2; heart rate- 64/min, blood pressure -120/70 mmHg; no pallor, icterus or clubbing. **Laboratory results:** On investigation, complete blood count (CBC), blood sugar, liver and renal profile was within normal range. Deranged lipid profile (triglyceride 324 mg/dl, total cholesterol – 290 mg/dl) was present. The thyroid function tests (TFT) and other related tests were as follows:- Thyroid-stimulating hormone (TSH): 7.0 µIU/L (ref range 0.4 - 4.12 µIU/L) High, FT3: 1.6 pg/mL (ref range 2.5 - 3.9 pg/mL) Low , FT4: 0.62 ng/dL (ref range 0.6 - 1.3 ng/dL), thyroid peroxidase antibodies (TPOAb): 5.3 IU/mL(ref range <9.0 IU/mL), thyroglobulin antibodies (TgAb): 2.7 IU/mL (ref range <4.0 IU/mL). **Diagnosis:** As the TSH concentration was elevated and FT3 level was low with no evidence of an autoimmune disorder, a diagnosis of primary hypothyroidism was given. **Treatment outcome and follow-up:** AT was started on levothyroxine 50 mcg/day and results of TFT repeated after 4 weeks. There was mild symptomatic improvement, but TFT was not normal. Levothyroxine dose was increased to 75 mcg/day and subsequently to 100 mcg/day and 125 mcg/day based on TSH value till patient became biochemically euthyroid and symptom resolution was noted. Patient was advised to maintain minimum four hours between intake of levothyroxine and calcium carbonate tablet. The levothyroxine dose was reduced to 100 mcg/day and repeat TFT after 4 weeks shown euthyroid state. The results of TFTs before and after treatment initiation are given in Table 1 and Figure 1.

Table 1. Thyroid function test results of case no. 1 (AT).

Parameter (Ref range)	Baseline	After 4 weeks (50 mcg/day)	After 4 weeks (75 mcg/day)	After 4 weeks (100 mcg/day)	After 4 weeks (125 mcg/day)	After 4 weeks (100 mcg/day)
TSH (mIU/L) (0.4 - 4.12)	7.0	6.2	5.8	4.6	3.8	3.2
Free T3 (pg/mL) (2.5 - 3.9)	1.6	2.2	2.4	2.7	3.1	3.3
Free T4 (ng/dL) (0.6 - 1.3)	0.62	0.68	0.70	0.71	0.82	0.98

TSH -thyroid-stimulating hormone, T3- Triiodothyronine, T4- thyroxin

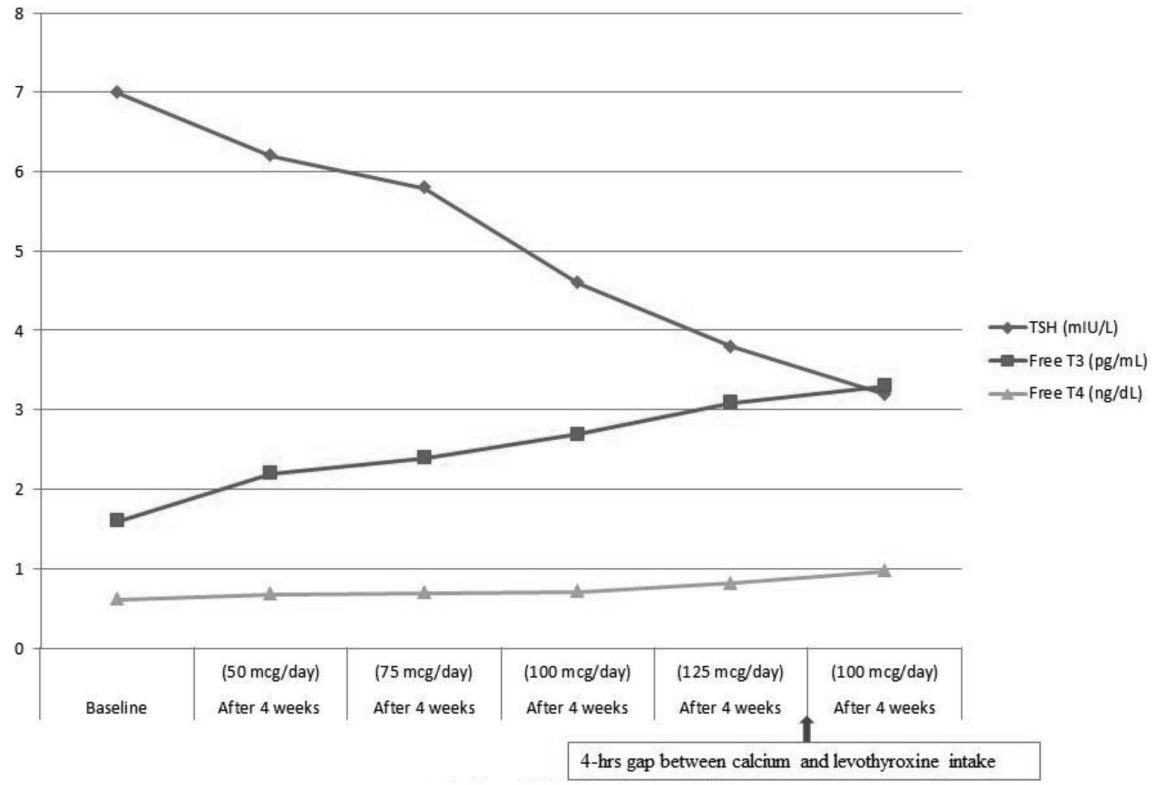

Figure-1: Line graph depicting variation in thyroid function tests with levothyroxine dosage(Case-1)

Discussion: The interaction only applies to orally administered thyroid products (mainly levothyroxine) and orally administered calcium salts (mainly calcium carbonate), requiring therapy modification. Calcium salts may diminish the therapeutic effect of thyroid products. For optimum effect, separation in the doses of the thyroid product and the oral calcium supplement by at least 4 hours is required. TSH significantly increased and both free and total T4 decreased with concurrent administration of calcium carbonate (1200 mg/d of elemental calcium) in a prospective cohort study of 20 patients previously stabilized on levothyroxine (19). After discontinuation of calcium carbonate, TSH and T4 values returned towards baseline (19). Similarly, a study in 8 healthy volunteers reported a 20-25% decrease in levothyroxine absorption associated with concurrent ingestion of calcium carbonate, calcium citrate, and calcium acetate (500 mg of elemental calcium each) (20). Several case reports also described increase in TSH values and/or decrease in T4 associated with concurrent use of calcium carbonate in patients previously stabilized on levothyroxine (21-25). In a database analysis, median serum TSH concentrations were 0.27 mIU/L greater in the 6 months following calcium initiation compared to the year (compared to previous year 26). TSH concentrations following calcium initiation increased by at least 5 mIU/L in 4.4% of patients, and decreased by at least 5mIU/L in 3.3% of patients. The mechanism of this interaction appears to be due to adsorption of levothyroxine to calcium in the GI tract. An in vitro study confirmed that in acidic conditions, levothyroxine does adsorb to calcium carbonate (19). Reports that separation of calcium carbonate and levothyroxine administration successfully avoids the interaction lend further support to this as the mechanism (23). The degree to which other thyroid products and/or other calcium products are at risk for this interaction is unclear. In contrast to one study of healthy volunteers that found a similarly significant interaction with calcium carbonate, calcium citrate, and calcium acetate, one analysis has concluded that calcium acetate may be associated with a lower interaction risk than calcium carbonate (20,27). In a study of 67 hemodialysis patients receiving levothyroxine together with a phosphate binder, those patients receiving calcium carbonate had significantly higher TSH values than those patients receiving calcium acetate (26).

Take home message: As a physician, we should monitor for decreased therapeutic effects of thyroid products if an oral calcium supplement is initiated/dose increased, or increased effects if an oral calcium supplement is discontinued/dose decreased. Alternatively, a gap of four hours may be maintained between intake of levothyroxine and calcium supplements.

Case presentation 2

SS, 52-year-old female, presented with complaints of fatigue, weight gain, constipation and cold intolerance. She stated that her weight has gradually increased (approx. 12 kg in last six months) despite no change in her activity level or eating habits. The only medication she takes is an omeprazole/ pantoprazole daily for dyspepsia. On physical examination, body mass index (BMI) was 31.4 kg/sqm; heart rate- 68/ min, blood pressure -116/76 mmHg; no pallor, icterus or clubbing. **Laboratory results:** On investigation, complete blood count (CBC), blood sugar, liver and renal profile were within normal range. The thyroid function tests (TFT) and other related tests were as follows:- TSH: 8.8 µIU/L (ref range 0.4 - 4.12 µIU/L) High, FT3: 1.1 pg/mL (ref range 2.5 - 3.9 pg/mL) Low , FT4: 0.60 ng/dL (ref range 0.6 - 1.3 ng/dL), TPOAb: 5.1 IU/mL (ref range <9.0 IU/mL), TgAb: 2.4 IU/mL (ref range <4.0 IU/mL). **Diagnosis:** As the TSH concentration was elevated and FT3 level was low with no evidence of an autoimmune disorder, a diagnosis of primary hypothyroidism was given. **Treatment outcome and follow-up:** SS was started on levothyroxine 50 mcg/day and results of TFT repeated after 4 weeks. There was mild symptomatic improvement, but TFT was not normal. Levothyroxine dose was increased to 75 mcg/day and subsequently to 100 mcg/ day based on TSH value till patient became biochemically euthyroid and symptom resolution was noted. Patient was advised to take pantoprazole as on need basis and minimum four hours gap to be maintained between intake of levothyroxine and pantoprazole. The levothyroxine dose was reduced to 75 mcg/day and repeat TFT after 4 weeks shown euthyroid state. The results of TFTs before and after treatment initiation are given in Table 2 and Figure 2.

Table 2. Thyroid function test results of case presentation

Parameter (Ref range)	Baseline	After 4 weeks (50 mcg/day)	After 4 weeks (75 mcg/day)	After 4 weeks (100 mcg/day)	After 4 weeks (75 mcg/day)
TSH (mIU/L) (0.4 - 4.12)	8.8	7.4	6.3	4.0	3.1
Free T3 (pg/mL) (2.5 - 3.9)	1.1	1.3	2.1	2.9	2.8
Free T4 (ng/dL) (0.6 - 1.3)	0.60	0.86	0.89	0.96	1.2

TSH -thyroid-stimulating hormone, T3- Triiodothyronine, T4- thyroxin

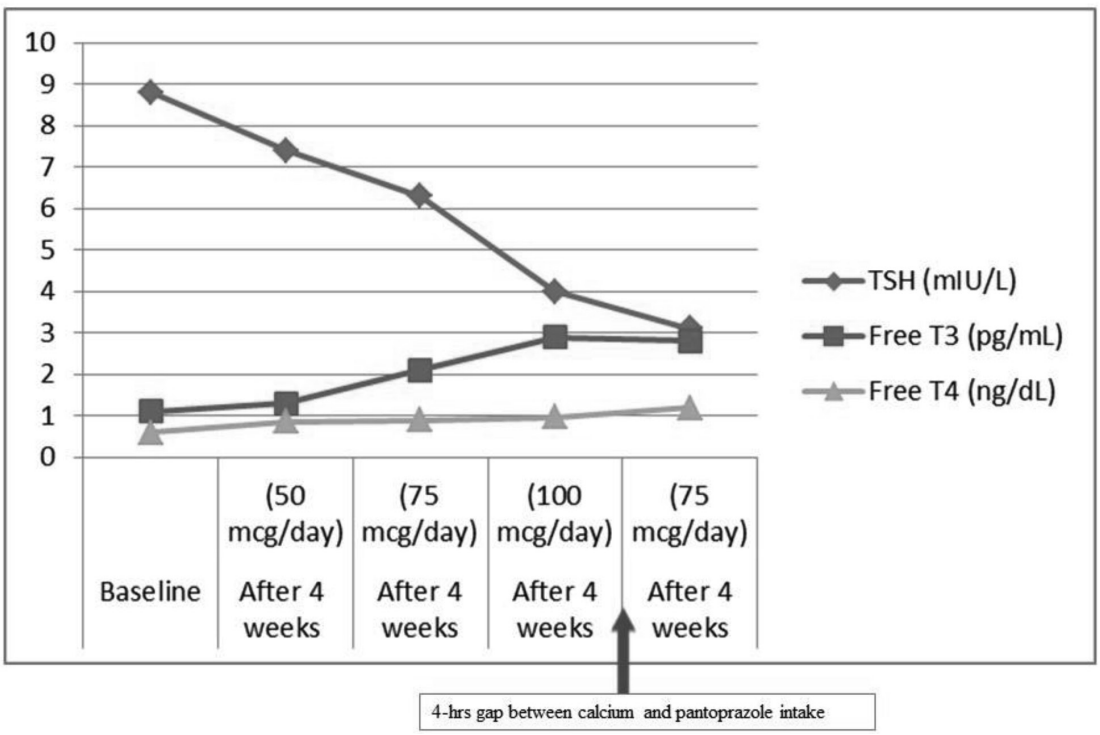

Figure-2: Line graph depicting variation in thyroid function tests with levothyroxine dosage(Case-2)

Discussion: Inhibitors of the Proton Pump (Proton pump inhibitors - PPIs and Potassium competitive acid blockers - PCABs) like Dexlansoprazole, Esomeprazole, Ilaprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole, Revaprazan, S-Pantoprazole and Vonoprazan etc. may decrease the serum concentration of thyroid products. Existing data/reports are inconsistent. One study enrolled 123 patients treated with levothyroxine for nontoxic multinodular goiter who also displayed clinical features suggestive of reduced gastric acid secretion (e.g. Helicobacter pylori or atrophic gastritis) and compared them with 135 control patients treated with levothyroxine with no signs of reduced gastric acid secretion. In order to maintain the desired thyroid-stimulating hormone (TSH) concentration, daily doses of levothyroxine were 22% to 34% higher in patients with reduced acid secretion compared with patients with unchanged gastric acidity. As an additional analysis, 10 patients had their TSH and levothyroxine doses evaluated before and after treatment with omeprazole 40 mg daily. Similar to overall trial results, levothyroxine doses were 37% higher during omeprazole therapy in order to maintain similar TSH levels (28). A retrospective analysis compared 37 patients receiving stable levothyroxine doses for 6 months who subsequently were started on lansoprazole with 55 control patients on stable levothyroxine doses who did not receive proton pump inhibitor (PPI) therapy (29). TSH levels increased 30% in patients who received lansoprazole and were essentially unchanged (less than a 6% change) in control patients. In a database analysis, median serum TSH concentrations were 0.12 mIU/L greater in the 6 months following PPI initiation compared with the previous year in 887 patients receiving stable levothyroxine doses (30). TSH concentrations following PPI initiation increased by at least 5 mIU/L in 5.6% of patients, and decreased by at least 5 mIU/L in 3.2% of patients. In contrast, one pharmacokinetic study found no change in TSH or the AUC of thyroxine (T4) or free-T4 when levothyroxine (4 mcg/kg single dose) was given after pantoprazole therapy (40 mg daily for 7 days) (31). Another study (N=30) found no change in levothyroxine (600 mcg single dose) absorption or the AUC of T4 when administered following a 7 day course of esomeprazole (40 mg daily) or famotidine (20 mg twice daily) (32). Similarly, in another study of 19 patients receiving a stable dose of levothyroxine and whose TSH levels were maintained for one year at least prior to start of (33). The proposed mechanism of this potential interaction is impairment of thyroid product absorption in the presence of elevated gastric pH. However, thyroid product absorption is variable and influenced by numerous factors (e.g. age, dietary habits, concomitant disease states, interacting medications) (28). It is unknown what role these factors may have played in the results of the analyses suggesting an interaction between PPIs and thyroid products since those analyses were either retrospective or not specifically designed to assess this interaction. Other data have suggested that a drug interaction between these agents is dependent on use of one or more specific levothyroxine tablet formulations (34). However, the findings and generalizability of all analyses suggesting an interaction are questionable because the two pharmacokinetic studies investigating the interaction found no impact of PPI or other gastric-acid-reducing treatment on thyroid product absorption. Because potassium-competitive acid blockers (PCABs) are pharmacologically similar to PPIs, they are expected to interact similarly.

Take-home message: Interaction between proton pump inhibitors and decreased levothyroxine absorption is inconsistent as some studies have reported that PPI increases TSH level but pharmacokinetic studies have shown no impact of PPI on thyroid product absorption. However, it's worthwhile to deprescribe PPI and see its impact on TSH levels in patient receiving high doses of levothyroxine for achieving a euthyroid state.

Conclusion

Concomitant medications can inhibit the absorption of levothyroxine, probably by binding with levothyroxine in the gut or increasing its metabolism. In addition to compliance, it is important to maintain a high index of suspicion about drug-drug interaction with concomitant medications (prescribed and non-prescribed) when thyroid function test results and symptoms of the patient not improving with sufficiently adequate dosage of levothyroxine. As a physician, it should be our endeavor to ensure that more people with hypothyroidism are given effective treatment, and to work out the best way to use levothyroxine (deprescribing if possible or by maintaining a gap of at least 4 hours between ingestions) so that patients get the best results. If the health provider has difficulty titrating the correct dose of levothyroxine to normalize TSH, the patient should be referred for consultation with a clinical pharmacologist/pharmacist. Most of the drug-drug interactions are preventable.

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