



Over-the-counter protein supplement resulting in impaired thyroxine absorption in a hypothyroid patient

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Summary

Whey protein is a popular dietary supplement that is claimed to provide multiple health benefits. It has been shown to delay gastric emptying and impair ileal nutrient absorption. Additionally, some of the other additives like papain enzyme, soy lecithin in these protein supplements could interfere with L-thyroxine absorption. There is no evidence in the literature for the effects of protein supplements on L-thyroxine absorption. Herein, we describe a case of a 34-year-old lady who was on endocrinology follow up for primary hypothyroidism with stable thyroid-stimulating hormone (TSH) levels within the normal range while on L-thyroxine with a dose of 125 µg daily for the last 3 years, presenting with mild hypothyroid symptoms and elevated TSH level following a recent introduction of a protein supplement by her physical care adviser. Her treatment adherence and ingestion technique were good throughout, she was not on other medications or herbal remedies, there were no other changes in her food pattern or features suggestive of malabsorption, she was not pregnant, was taking the same L-thyroxine brand and TSH test was done from the routine lab. Since the only factor which could have contributed to the deranged TSH levels was the recent introduction of the whey protein supplement, we advised her to stop the protein supplement while continuing the same dose of L-thyroxine. Her TSH level was repeated in 6 weeks and was found to be normal (1.7 mIU/L). Our case report demonstrates that over-the-counter protein supplements could interfere with L-thyroxine absorption. Therefore, patients on L-thyroxine should be cautious when taking them.

Learning points:

- Over-the-counter protein supplements could interfere with oral L-thyroxine absorption.
- The underlying mechanism could be the effect of whey protein by delaying gastric emptying and reduced responsiveness of organic anion transporters in the ileum, and there may be a contribution from other additives like papain and soy lecithin present in these supplements.
- When there is an elevation of previously stable thyroid-stimulating hormone (TSH) value in a hypothyroid patient on oral L-thyroxine, the patient's assessment should include inquiring for a recent introduction of protein supplement, in the absence of other well-known risk factors.
- Discontinuation of protein supplement results in normalization of thyroid function tests.
- Patients on oral L-thyroxine should be cautious when taking over-the-counter protein supplementation.

Background

In recent years, milk constituents have become recognized as functional foods, suggesting their use has a direct and measurable effect on health outcomes. Whey protein, a protein complex derived from milk is being promoted as a functional food with a number of health benefits (1). There is no evidence in the literature for the effects of protein supplements on L-thyroxine absorption and TSH levels in hypothyroid patients. Studies have shown that whey proteins delay gastric emptying time (2). Additionally, it may interfere with thyroid hormone transporters in the intestine (3, 4). Apart from that, papain and soy lecithin are included as additives in these supplements. While these mechanisms could be contributory to the impaired L-thyroxine absorption in the presence of the whey protein supplement, the exact mechanism is inconclusive. Our case study describes an unexpected effect of over-the-counter protein supplementation in a hypothyroid patient on oral L-thyroxine supplementation.

Case presentation

A 34-year-old lady was on endocrinology follow up for primary hypothyroidism. She was diagnosed with having Hashimoto's thyroiditis with mildly elevated anti-thyroperoxidase antibody titre since the last 3 years, 10 years following the remission of graves' disease at which time her thyroid receptor antibody level was negative. Her serum TSH levels were stable and within the normal range over the last 3 years while she was on oral tablet form of L-thyroxine with a dose of 125 µg daily (1.66 ug/kg/day dose for her weight of 75 kg). Her last TSH value in April 2019 was 1.6 mIU/L. After six monthly reviews, in November 2019, she had mild hypothyroid symptoms for the last 1 month, and her TSH was elevated to 12.5 mIU/L. Her daily treatment adherence was good throughout and denied any recently missed doses. She adhered to proper ingestion technique with ingestion on an empty stomach and delaying breakfast for 1 h after taking her L-thyroxine. She did not have other comorbidities and was not on other prescribed or over-the-counter medications or herbal remedies, but she was recently prescribed a protein supplement by her physical care adviser for the purpose

of improving the muscle strength. It was a whey protein blend with whey concentrate and whey isolate of which she was taking one serving (30 g with 22 g protein) daily 30 min after breakfast for the last 2 months. In addition to the whey protein concentrate and isolate, the supplement consisted of taurine, flavours (banana, cream), sodium chloride, dextrose, L-glutamine, thickener (xanthan gum), sweeteners (acesulfame K, sucralose), L-leucine, emulsifier-soy lecithin, digestive enzymes; bromelain and papain.

There was no change in her food pattern like an increase in consumption of coffee, soymilk or grapefruit juice except adding the whey protein supplement. She also denied a recent change of her L-thyroxine brand. She did not have any recent onset dyspepsia, vomiting, diarrhoea, loss of weight or anaemia. She did not have a period of amenorrhoea suggestive of pregnancy or recent onset of significant weight gain. Her TSH test was done from the same lab which uses a chemiluminescent immune assay.

Since the only factor that could be elicited from detailed inquiry, which could have contributed to the recently deranged TSH, was the recent introduction of the whey protein supplement, we advised her to stop the protein supplement while continuing the same dose of L-thyroxine. Her TSH level was repeated in 6 weeks in January 2020 and was found to be normal (TSH - 1.7 mIU/L).

Investigation

Her last TSH value in April 2019 was 1.6 mIU/L. In November 2019, her TSH value elevated to 12.5 mIU/L after the recent initiation of the protein supplement. In January 2020, her TSH value returned to 1.7 mIU/L after stopping the protein supplement (Fig. 1).

Outcome and follow up

On her follow-up assessment in 6 months, the TSH value remained normal.

Discussion

Oral L-thyroxine is the mainstay of treatment of hypothyroidism and is being administered with a mean

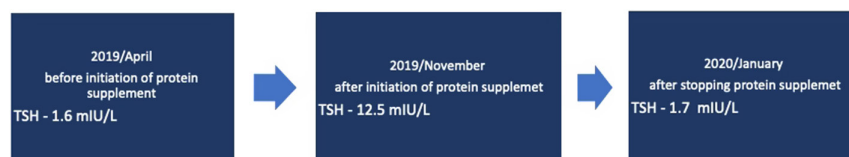


Figure 1
TSH variation over time.



treatment dosage of 1.6–1.8 µg/kg/day (5). About 60–80% of the oral dose of L-thyroxine is absorbed when taken on an empty stomach without interfering with food or medication. Absorption occurs within 2–3 h of ingestion and occurs mainly in the jejunum and ileum. Adequate gastric acidity is required to dissolve salt-based tablets including L-thyroxine allowing for proper intestinal absorption (5, 6, 7). Patient's biochemical response to L-thyroxine treatment is determined by their serum TSH level (8), and TSH is the best marker for assessing the adequacy of treatment (5).

Factors that affect the ability to maintain TSH within the desired level include variable patient adherence, gastrointestinal conditions that affect L-thyroxine absorption, medication and food that interfere with L-thyroxine absorption, as well as the timing of meals, medications and physiological conditions that increase the demand for L-thyroxine and storage conditions that affect the integrity of the tablet (7, 8, 9). Gastrointestinal malabsorption has been recently extensively reviewed by Camilla Virili *et al.* (7). Gastroparesis leading to delayed gastric emptying has also been recently recognized as a cause of persistently elevated TSH level in hypothyroidism (7, 10, 11). The absorption of L-thyroxine can also be affected by different formulations due to various inactive ingredients present in different brands (12). Although uncommon, the possibility of analytical errors with 'sandwich' immune assays secondary to the interference of heterophilic antibodies that generate false-positive signal leading to falsely elevated TSH level should also be considered. But repeating TSH level using the same platform becoming normal will usually exclude assay interference (13).

The index patient was on 1.66 g/kg (125 µg) thyroxine dose throughout, which is in the range for those with minimal residual thyroid function, but it is considered to restore TSH level in the normal range in most of the patients with hypothyroidism (5). She had good adherence to L-thyroxine with correct ingestion technique with a 1-hour gap before breakfast that facilitated the optimum absorption. There were no other features to suggest GI malabsorption or maldigestion condition, and she was not on any interfering medication or food. The basal thyroxine dose required by a patient depends on residual thyroid function, weight, lean body mass and to a lesser magnitude on patient's age, sex and menopausal state. Additionally, the bioequivalence of different thyroxine preparations may differ slightly between brands (5). Given the fact that she was maintaining the normal TSH level with the same dose and the brand of thyroxine, the basal upper normal

range dose requirement in the presence of Hashimoto's thyroiditis could be due to her overweight or the difference in the bioequivalence of her thyroxine preparation.

For her recent presentation with elevated TSH level while on the same dose, brand and adherence, the only factor we could find that could have interfered with her L-thyroxine absorption was the protein supplement. After omitting the protein supplement from her diet, repeat TSH level returned back to normal confirming that the protein supplement interfered with her L-thyroxine absorption. To our knowledge, this is the first case report showing that an over-the-counter protein supplement can interfere with L-thyroxine absorption.

In recent years, milk constituents have become recognized as functional foods, suggesting their use has a direct and measurable effect on health outcomes. Whey protein, a protein complex derived from milk is being promoted as a functional food with number of health benefits (1). Whey proteins have all the essential amino acids in a high concentration, particularly high concentration of branched chain amino acids (especially leucine) which are important for tissue growth and repair and improved exercise performance and enhancement. The main components of whey protein include beta-lactoglobulin, alpha lactalbumin, lactoferrin, immunoglobulins, lactoperoxidase enzymes, glycomacropetides, lactose and minerals (14).

Advances in processing techniques resulted in the development of several different finished whey products like whey protein concentrates (ranging from 80–95% protein), reduced lactose whey, whey protein isolate (90–95% protein), demineralized whey, and hydrolyzed whey (1). These different commercially available whey protein products vary in the amount of protein, carbohydrates, immunoglobulins, lactose, minerals and fat that they contain and also the type and amount of additives. In addition to whey protein components, these protein supplements commonly contain other additives, where our patient's supplement had taurine, flavour (banana, cream), sodium chloride, dextrose, L-glutamine, thickener (xanthan gum), sweeteners (acesulfame K, sucralose), L-leucine, esterifier – soy lecithin, digestive enzyme blends – bromelain and papain (12 mg each per 30 g serving). In this case, impaired L-thyroxine absorption could be due to the effects of whey protein itself or the combined effect of the additives of the protein supplement.

Studies have shown that whey protein delays gastric emptying time. Stanstrup *et al.* have demonstrated that following a whey meal, plasma levels of acetaminophen and its metabolites rose markedly more slowly, and the



maximum plasma concentration and the time taken to reach maximum plasma concentration fell significantly compared with other meals containing casein, gluten and fish protein (2). Oberoi *et al.* have clearly shown that there is a significant delay in gastric emptying following whey protein drink compared to controls found by measuring gastric antral area by 2D ultrasonography and calculating gastric emptying rates based on those measurements (15). Also, studies have shown that the gastric inhibitory peptide (GIP) which is released in response to food reaching the proximal small intestine was showing lower levels for the first hour after a whey protein meal, further supporting that whey protein delays gastric emptying (16). Delayed gastric emptying by medications and gastroparesis has clearly been shown to impair L-thyroxine absorption (10, 11, 17). The underlying mechanism may be sequestration of appropriately administered L-thyroxine dose with subsequent meals due to delayed gastric emptying, leading to decreased absorption (11). Though it has been suggested that lower intestinal motility increases the exposure time of thyroxine to the intestinal mucosa and promotes absorption (7), evidence is lacking for whey protein's effect on intestinal motility.

L-thyroxine hormone absorption can be reduced when it is co-administered with a variety of different substances, and studies have shown that concurrent cow's milk ingestion impairs thyroxine absorption likely attributable to the effect of its calcium and protein content (18). Though there was a time gap of 1.5 h between ingestion of thyroxine tablet and intake of whey protein supplement in the presented case, binding of whey protein to thyroxine leading to decreased thyroxine absorption is a possibility given the fact that the whole absorption process takes up to 2–3 h despite peak absorption occurring in the first 90 min (7). This could be exacerbated as a consequence of whey protein-induced delayed gastric emptying.

In addition, Kanishka N Nilaweera *et al.* suggested that whey protein reduces the responsiveness of ileal nutrient transporters to nutrient availability in lumen over time (3). The molecular mechanisms of L-thyroxine absorption in the gastrointestinal tract is still partially understood. Different thyroid hormone transporters are expressed in different organs mediating cellular uptake of thyroid hormones of which OATP2B1 (organic anion transporting polypeptide) being an important transporter expressed in enterocytes involving in thyroid hormone and anionic drug intestinal absorption. L-thyroxine drug/food interactions may result from interaction with these transporters (4, 19). Grapefruit juice has been shown to inhibit this transporter *in vitro* and the effect of grapefruit

juice in reduced L-thyroxine absorption is postulated due to this mechanism (20). Likewise, there could be a whey protein-mediated inhibitory effect on these thyroid hormone transporters interfering with L-thyroxine absorption, as its effect on ileal nutrient transporters. But this hypothesis needs further studies to prove it.

Among the additives in the protein supplement in the current study which could have an effect on L-thyroxine absorption include papain and soy lecithin. Soy lecithin is one of the most ubiquitous additives in the food supply, used primarily as an emulsifier. It contains about 35% soybean oil and 16% phosphatidylcholine and the remaining percentage is other phospholipids and glycolipids (21). It usually makes up no more than 1% of processed foods. Thus, for a single serving of 30 g of the protein supplement, the estimated amount of soy protein ingested is < 0.1 g. In the literature, persistent TSH elevation in hypothyroid patients in association with concomitant soy ingestion was associated with either soy formula, soy protein supplement or soy diet which contained a higher percentage of soy protein (22, 23, 24). Apart from that, Persiani *et al.* have revealed that post-menopausal hypothyroid women who were given a dietary supplement containing 60 mg of isoflavone, a phytoestrogen in soy protein that has claimed to interfere with thyroid functions (25), has not affected L-thyroxine absorption (26) where the isoflavone content in isolated soy protein is up to 1 mg/g of protein (27). Considering these, it is unlikely that the presence of soy lecithin being a major contributor to the impaired thyroxine absorption. Deiana *et al.* have reported a case of daily intake of a large amount of papaya fruit for 2 weeks (five to six fruits daily) resulting in impaired effectiveness of L-thyroxine therapy with the development of mild hypothyroidism (28). The possible mechanism they have suggested is a reduction of gastric acid secretion by papain acting directly on the gastric mucosa. Besides that, they have suggested possible effects from several other papaya substances as well. Thus, the papain enzyme included in the protein supplement could interfere with L-thyroxine absorption due to its effect on gastric acidity. However, this effect might be minimal with the amount of 12 mg per serving where the approximate yield of papain is 5 g per unripen fruit (29). Lactose that could be present in variable fractions with whey products is not known to cause significant interference on L-thyroxine absorption in the absence of features of lactose intolerance.

Our case report shows that over-the-counter protein supplements could interfere with L-thyroxine absorption. The aforementioned could be considered as an explanatory hypothesis for the impaired L-thyroxine



absorption in the presence of over-the-counter protein supplements. More studies are required to assess the exact effect of whey protein supplements on L-thyroxine absorption. Patients on L-thyroxine should be cautious when taking over-the-counter protein supplementation. Based on previously discussed facts, shifting the protein supplement to a later part of the day (>4 h since ingestion of thyroxine) would be an alternative to minimize its effects on L-thyroxine absorption, but it needs to be confirmed by further studies.

Patient's perspective

The patient stated that she never thought that the over-the-counter protein supplement could have interfered with her oral thyroxine absorption. But timely identification of it as the culprit for the derangement of her previously stable thyroid function made her restore the thyroid function without unnecessary dose increments and investigations. Additionally, she stated that she would be more cautious when going for an over-the-counter supplement while on replacement with important medication like thyroxine in the future.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent for publication of her clinical details was obtained from the patient.

Author contribution statement

C N A proposed the original idea for this case report. P A D M K drafted the manuscript. C N A and N S K critically reviewed the manuscript. P A D M K revised the manuscript into its final version.

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