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Case report

Worsening of Congenital Hypothyroidism After Start of Carob-bean Gum Thickened Formula: Is There a Link? A Case Report

Signorino C et al. Congenital Hypothyroidism and Carob-bean Gum Thickened Formula

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What is already known about this topic?
It is known that soy infant formulas, as well as soy-containing baby foods, some drugs used to manage infants with recurrent regurgitation and specific medications for infant colic, are related to altered thyroid function in early childhood. Moreover in literature it is described that carob beans thicken formula milk increased its viscosity and thickened formula with locust (carob) bean gum, slows gastric emptying in infants**.**

What this study adds to the literature?
Our case report is the first to evidence the possible effect of the carob-bean gum thickened formula on L-T4 absorption, recommending caution and frequent thyroid function evaluation if these products are given to patients with CH.

Abstract
Congenital hypothyroidism (CH), if not correctly treated with L-thyroxine (L-T4), may be responsible for a permanent intellectual disability. If patients treated with L-T4 do not achieve a good TSH control, the possibility of poor compliance and/or poor absorption of L- T4 should be investigated. We describe an infant with CH whose thyroid hormone levels worsened after she started a carob-bean gum thickened formula. A baby girl was diagnosed with CH by newborn screening (at confirmatory blood evaluation TSH was 496.0 µIU/mL and FT_4 0.13 ng/dl). Five weeks after beginning $L\text{-}T_4$ treatment TSH normalized (TSH 2.72 µIU/mL , FT_4 2.08 ng/dl); nevertheless, only another 5 weeks later we noticed a new worsening of thyroid hormone levels (TSH 31.1 µIU/mL , FT_4 1.27 ng/dl), which worsened further (TSH 44.8 µIU/mL, FT_4 1.16 ng/dl) even if $L\text{-}T_4$ dosage was increased. Anamnesis disclosed that she had been given a carob-bean gum thickened formula to combat gastroesophageal reflux disease (GERD) rather than regular type 1 formula milk. The anti-reflux milk formula was discontinued and after 14 days the patient's TSH level dropped to 0.38 µIU/mL and FT_4 increased to 2.68 ng/dL, allowing the $L\text{-}T_4$ dosage to be reduced. Carob-bean gum thickened formula may influence the absorption of $L\text{-}T_4$. If such formulas are used, we recommend a more frequent evaluation of thyroid function. In CH infants, inexplicably high TSH levels could be caused by gastrointestinal disorders or the interference of drugs or other substances, including some types of milk formula, which impair $L\text{-}T_4$ absorption.
Keyword: Congenital hypothyroidism; L-thyroxine; treatment; carob-bean gum thickened formula; gastro-intestinal absorption; gastroesophageal reflux; case report

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Introduction
Congenital hypothyroidism (CH) is a relatively frequent endocrine disorder in which thyroid hormone (TH) deficiency, if not promptly diagnosed and correctly treated with L-thyroxine (L-T4), may lead to permanent intellectual disability (ID) (1). Below 3 years of age, adequate TH levels are essential for normal brain development. In CH patients treated with L-T4, poor compliance and/or poor absorption of L-T4 may cause a reduced developmental outcome compared to patients with satisfactory compliance and uncompromised absorption (2). To achieve better developmental outcome, thyroid hormones should return to normal range rapidly, preferably within the first 14 days of therapy (2). Screening programs for CH are applied in many countries, allowing L-T4 treatment to be started early, generally when the disease is still asymptomatic (1); high starting doses of L-T4 are the treatment of choice and determine both auxological (3) and neurological improvement (4). Nevertheless, initial L-T4 dose should vary based on formulation used, thyroid-stimulating hormone (TSH) and TH values (5).
In the presence of poor TSH control, it is advisable to first investigate the correct method of administration and intake of L-T4, since caregivers make mistakes that can often be identified (2).
Gastrointestinal diseases as well as several medications and other substances may affect the L-T4 absorption in infants (2,6). Proton-pump inhibitors, aluminium-containing antacids, iron and calcium salts, herbal remedies and nutritional supplements may worsen L-T4 absorption, modifying gastric pH or binding with L-T4 to create insoluble complexes (2,7,9,10). Although few data have been reported in the literature, there could also be interference from infant milk formula, which, due to its composition rich in fats, proteins and lactose, does not allow L-T4 to be absorbed in the small intestine (8). In a small number of historic case reports, soy infant formulas and soy-containing baby foods are considered responsible for the alteration of TH absorption in the first years of life (11). After weaning, if L-T4 is taken with food, a higher dose may be needed to maintain euthyroidism (5,8).
The liquid formulation of L-T4 is currently the most used in children with CH, given the greater absorption of the oral solution compared to the solid one (12). Differently, some L-T4-treated children with CH achieve euthyroidism only if they are treated with a combined therapy of L-T4 and liothyronine (L-T3), probably due to an insufficient amount of thyronine (T3) produced by the peripheral conversion of thyroxine (T4) (13).
Endocrinologists and pediatricians must appropriately inform parents about the correct method of L-T4 administration and the possible interference of some drugs, supplements and foods. Parents also need to be made aware of the potential negative consequences for the growth and the neurological development of their child in case of erroneous intake of the medication (10). Thickened formulas are

increasingly used in patients with gastroesophageal reflux. Availability of calcium, iron, and zinc tends to be significantly impaired by products thickened with locust bean gum compared to non-thickened infant formulas (14).
In this case report we described for the first time an infant with CH whose TH levels worsened after a carob-bean gum thickened formula was introduced for gastroesophageal reflux disease (GERD) and discuss the possible interferences of the infant milk formula with L-T4 treatment.

Case presentation

A baby girl was diagnosed with CH by newborn screening with a blood spot on filter paper (TSH =186.57 µIU/mL). At the first evaluation, anamnesis showed that the patient was born to non-consanguineous, healthy, young parents. There was no family history of thyroid disorders. Pregnancy was uncomplicated and the child was born by cesarean delivery at 39 weeks of gestation. Her birth weight was 3,140 g (-0.36 SDS, according INeS chart, 2010), length 49.0 cm (-0.41 SDS, according INeS chart, 2010) and head circumference 34.5 cm (0.44 SDS, according INeS chart, 2010). Apgar score 9I – 9V. Clinical examination (at 8 days of age) revealed icterus, little spontaneous motor activity, a hoarse cry and cool, dry, rough and thick skin. Her abdomen was distended with an umbilical hernia. At that time she was fed breast milk supplemented with regular type 1 formula milk (80 ml for seven meals a day). At the confirmatory blood evaluation (at 8 days of age) TSH was 496.0 µIU/mL (normal value for age: 0.70 – 11.0 µIU/mL), free T4 (FT4) was 0.13 ng/dl (normal value for age: 1.24 - 3.89 ng/dl), and free T3 (FT3) 1.05 pg/mL (normal value for age: 2.73 - 8.46 ng/dl); anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin and TSH receptor antibodies (TRAbs) were negative. Iodine urinary excretion was normal. Ultrasound examination of the neck was consistent with thyroid agenesis (Figure 1).
The patient immediately started therapy with 32.2 µg/day (10.6 µg/kg per day) of liquid L-T4. After 5 weeks of L-T4 treatment, TSH values normalized (2.72 µIU/mL; normal value: 0.40 – 4.0 µIU/mL) with free T4 values (FT4) of 2.08 ng/dl (normal value for age: 1.24 - 3.89 ng/dl). However, only 5 weeks later blood tests revealed lower FT4 values (1.27 ng/dl) associated with a significant increase in TSH (31,1 µIU/mL), without any clinical findings of hypothyroidism and an anamnesis negative for poor compliance. Furthermore, parents ensured that they waited at least 30 minutes between the milk meal and the administration of L-T4. Consequently, the L-T4 dosage was raised to 50.0 µg/day (10.1 µg/kg per day) in line with the patient's increased body weight. After 1 week, TSH increased again (44.8 µIU/mL; normal value: 0.40 – 4.0 µIU/mL), while FT4 decreased (1.16 ng/dl; normal value for age: 0.8 - 1.9 ng/dl). The patient was not taking any medications other than levothyroxine. Anamnesis revealed that to supplement breast milk, the patient had been given a carob-bean gum thickened formula (170 ml for 7 meals a day) rather than regular type 1 formula milk for approximately three weeks as GERD treatment. When this anti-reflux milk was discontinued, after only two weeks, the patient's TSH level dropped to 0.38 µIU/mL, and her FT4 level increased to 2.68 ng/dL. L-T4 treatment was reduced (8.0 mcg/kg per day), with normalization of thyroid function (Figure 2).

Discussion

Our paper suggests that carob-bean gum thickened formula could influence the absorption of L-T_4, therefore caution in the use of these products in patients with CH is necessary. If such formula is used, we recommend evaluating thyroid function more frequently. To our knowledge this is the first case in literature reporting a potential interference of this type of anti-reflux milk on the absorption of L-T_4, therefore further studies are needed to confirm our finding.
Some drugs used to manage infants with recurrent regurgitation, such as acid lowering agents, increasing gastric pH, reduce the intestinal absorption of levothyroxine (15). With different mechanisms, specific medications for infant colic, such as simethicone, alter the bioavailability of levothyroxine (16).
Various thickening agents derived from cereals, such as polysaccharide from glass rice and carob bean gum, which are all sources of dietary fibre, are commonly used in the treatment of GERD and failure to gain weight in infants and children (17). Cow's milk formulas with added thickening agents (like carob beans or galactomannan) have long been commercially available. Carob beans thicken formula milk, increasing its viscosity. The beans have a high sugar content (48–56%, mainly sucrose, glucose, and fructose), and a low protein (3–4%) and fat content (0.2–0.6%). They are also rich in dietary fibre and minerals (e.g. Ca, Fe, etc) (18).
Milk thickening agents with carob bean gum improve clinical symptoms of GERD in infants (19), even if in rats some data show a reduction in the gastric emptying rate with a slowed passage of food from the stomach to the upper small intestine (20). In one study on infants with gastroesophageal reflux, a thickened formula with commercially available concentrations of locust (carob) bean gum slowed gastric emptying (21). Another study revealed a 1000-fold increase in meal viscosity, with a significative delay in gastric emptying (22). However, in a study involving 20 full term Thai infants without pathological gastroesophageal reflux there was no significance difference in gastric emptying half time (17). In adult humans, the addition of locust bean gum to a semisolid meal significantly delayed the gastric emptying rate (23).
To date the correlation between formula milk and L-T_4 absorption is not well clarified, however it would seem that composition of infant formula milk, rich in fat, protein and lactose, can reduce it. Consequently larger doses are required to maintain euthyroidism (7). One study reported that in adults, cow's milk can reduce the L-T_4 absorption by nearly 8%. There are no data in literature regarding breast milk, although it is possible that it decreases l-T_4 bioavailability (24-25).
The effect of soy infant formulas, as well as soy-containing baby foods, on thyroid function in early childhood is better understood (11,26-31). Soy-based formula is often an alternative to milk protein formula in cases of allergies or intolerances. Two historic case reports described two infants fed with soy-based formula, one of which with cretinism and goitre at 10 months of age, the other asymptomatic but with persistently high TSH levels despite large doses of L-T_4, both resolved after the suspension of the soy-based diet (11, 28). Other cases of soy-induced goitre in infants have been reported (29,30). Infants fed soy formula have prolonged increased of TSH when compared to infants on non-soy formula and they may need more frequent TSH measurements and increased L-T_4, doses to achieve a good control of thyroid function (31).
Certain herbal remedies and nutritional supplements contained in formula milk, including iron, calcium and fibre, can also impair L-T_4 absorption (2,32).
In conclusion, carob-bean gum thickened formula may influence the absorption of L-T_4.
Therefore, we recommended caution and frequent thyroid function evaluation if these products are given to patients with CH. In infants who need increasing doses of L-T_4, it is essential to investigate the method of administration and the medical history, including current medicines and diet, before modifying the drug dosage. Likewise, parents and caregivers should be informed about factors that may interfere with L-T_4 therapy in order to prevent or reduce potential damage.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written and signed consent has been obtained from the patient's parents.

Competing interests

The authors declare that they have no competing interests.

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Contributions

CS: She wrote the manuscript. MF: She collected the clinical and laboratory data. SS and GM: They reviewed the current guidelines, in order to write the discussion. CS: She collected the bibliography. SS: He reviewed the manuscript. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. CS, who wrote the manuscript, received no grant nor other form of payment to produce the manuscript. All authors read and approved the final manuscript.

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References

1. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. *Orphanet J Rare Dis.* (2010) 5:17. doi: 10.1186/1750-1172-5-17.
2. Stagi S, Municchi G, Ferrari M, Wasniewska MG. An Overview on Different L-Thyroxine (l-T4) Formulations and Factors Potentially Influencing the Treatment of Congenital Hypothyroidism During the First 3 Years of Life. *Front Endocrinol (Lausanne).* (2022) 13: 859487. doi: 10.3389/fendo.2022.859487.
3. Salerno M, Micillo M, Di Maio S, Capalbo D, Ferri P, Lettiero T, Tenore A. Longitudinal growth, sexual maturation and final height in patients with congenital hypothyroidism detected by neonatal screening. *Eur J Endocrinol.* (2001) 145(4):377-83. doi: 10.1530/eje.0.1450377.
4. Aleksander PE, Brückner-Spieler M, Stoehr AM, Lankes E, Kühnen P, Schnabel D, *et al.* Mean High-Dose l-Thyroxine Treatment Is Efficient and Safe to Achieve a Normal IQ in Young Adult Patients With Congenital Hypothyroidism. *J Clin Endocrinol Metab.* (2018) 103(4):1459-1469. doi: 10.1210/jc.2017-01937.
5. van Trotsenburg P, Stoupa A, Léger J, Rohrer T, Peters C, Fugazzola L, *et al.* Congenital Hypothyroidism: A 2020-2021 Consensus Guidelines Update-An ENDO-European Reference Network Initiative Endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. *Thyroid.* (2021) 31(3):387-419. doi: 10.1089/thy.2020.0333
6. Brito LNS, Andrade CLO, Alves CAD. Adhesion to Treatment by Children with Congenital Hypothyroidism: Knowledge of Caregivers in Bahia State, Brazil. *Rev Paul Pediatr.* (2021) 39:e2020074. doi: 10.1590/1984-0462/2021/39/2020074.
7. Centanni M, Benvenga S, Sachmechi I. Diagnosis and management of treatment-refractory hypothyroidism: an expert consensus report. *J Endocrinol Invest.* (2017) 40(12):1289-1301. doi: 10.1007/s40618-017-0706-y.
8. Virili C, Antonelli A, Santaguida MG, Benvenga S, Centanni M. Gastrointestinal Malabsorption of Thyroxine. *Endocr Rev.* (2019) 40(1):118-136. doi: 10.1210/er.2018-00168.
9. Skelin M, Lucijanić T, Amidžić Klarić D, Rešić A, Bakula M, Liberati-Čizmek AM, *et al.* Factors Affecting Gastrointestinal Absorption of Levothyroxine: A Review. *Clin Ther.* (2017) 39(2):378-403. doi: 10.1016/j.clinthera.2017.01.005.
10. Wiesner A, Gajewska D, Paśko P. Levothyroxine Interactions with Food and Dietary Supplements-A Systematic Review. *Pharmaceuticals (Basel).* (2021) 14(3):206. doi: 10.3390/ph14030206.
11. Wyk JJ, Arnold MB, Wynn J, Pepper F. The effects of a soybean product on thyroid function in humans. Pediatrics. (1959) 24:752-60. PMID: 13841160. Vigone MC, Ortolano R, Vincenzi G, Pozzi C, Ratti M, Assirelli V, et al. Treatment of Congenital Hypothyroidism: Comparison Between L-Thyroxine Oral Solution and Tablet Formulations Up to 3 Years of Age. Eur J Endocrinol (2021) 186(1):45–52. doi: 10.1530/EJE-20-1444
12. Vigone MC, Ortolano R, Vincenzi G, Pozzi C, Ratti M, Assirelli V, et al. Treatment of Congenital Hypothyroidism: Comparison Between L-Thyroxine Oral Solution and Tablet Formulations Up to 3 Years of Age. Eur J Endocrinol (2021) 186(1):45–52. doi: 10.1530/EJE-20-1444
13. Akcay T, Turan S, Guran T *et al.* T4 plus T3 treatment in children with hypothyroidism and inappropriately elevated thyroid-stimulating hormone despite euthyroidism on T4 treatment. Horm Res Paediatr. 2010;73(2):108-14. doi: 10.1159/000277627
14. Bosscher D, Van Caillie-Bertrand M , Van Dyck K , Robberecht H , Van Cauwenbergh R , Deelstra H. Thickening infant formula with digestible and indigestible carbohydrate: availability of calcium, iron, and zinc in vitro. *Journal of Pediatric Gastroenterology and Nutrition*, 01 Apr 2000, 30(4):373-378. doi: 10.1097/00005176-200004000-00005
15. G Ianiro, F Mangiola, T A Di Rienzo, S Bibbò, F Franceschi, A V Greco, A Gasbarrini. Levothyroxine absorption in health and disease, and new therapeutic perspectives. *Eur Rev Med Pharmacol Sci* 2014;18(4):451-6.
16. Balapatabendi M, Harris D, Shenoy SD. Drug interaction of levothyroxine with infant colic drops. *Arch Dis Child.* 2011 Sep;96(9):888-9. doi: 10.1136/archdischild-2011-300333.
17. Vivatvakin B, Buachum V. Effect of carob bean on gastric emptying time in Thai infants. *Asia Pac J Clin Nutr.*(2003) 12(2):193-7.
18. Papaefstathiou E, Agapiou A, Giannopoulos S, Kokkinofta R. Nutritional characterization of carobs and traditional carob products. *Food Sci Nutr.* (2018) 6(8):2151-2161. doi: 10.1002/fsn3.776.
19. Vandenplas Y, Sacré L. Milk-thickening agents as a treatment for gastroesophageal reflux. *Clin Pediatr (Phila).*(1987) 26(2):66-8. doi: 10.1177/000992288702600202.
20. Tsai AC, Peng B. Effects of locust bean gum on glucose tolerance, sugar digestion, and gastric motility in rats. *J Nutr.* (1981) 111(12):2152-6. doi: 10.1093/jn/111.12.2152.
21. Miyazawa R, Tomomasa T, Kaneko H, Morikawa A. Effect of formula thickened with locust bean gum on gastric emptying in infants. *J Paediatr Child Health.* 2006 Dec;42(12):808-12. doi: 10.1111/j.1440-1754.2006.00982.x
22. Marciani L, Gowland PA, Spiller RC, Manoj P, Moore RJ, Young P, Al-Sahab S, Bush D, Wright J, Fillery-Travis AJ. Gastric response to increased meal viscosity assessed by echo-planar magnetic resonance imaging in humans. *J Nutr.* 2000 Jan;130(1):122-7. doi: 10.1093/jn/130.1.122.
23. Darwiche G, Björgell O, Almér LO. The addition of locust bean gum but not water delayed the gastric emptying rate of a nutrient semisolid meal in healthy subjects. *BMC Gastroenterol.* 2003 Jun 6;3:12. doi: 10.1186/1471-230X-3-12.
24. Chon DA, Reisman T, Weinreb JE, Hershman JM, Leung AM. Concurrent Milk Ingestion Decreases Absorption of Levothyroxine. Thyroid. (2018) 28(4):454-457. doi: 10.1089/thy.2017.0428.
25. Roberts GW. Taking care of thyroxine. *Aust. Prescr.* (2004) 27:75-6. https://doi.org/10.18773/austprescr.2004.061.
26. Bhatia J, Greer F; American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. *Pediatrics.* (2008) 121(5):1062-8. doi: 10.1542/peds.2008-0564.
27. Hydovitz JD. Occurrence of goiter in an infant on a soy diet. N Engl J Med. (1960) 262:351-3. doi: 10.1056/NEJM196002182620707.
28. Pinchera A, Macgillivray MH, Crawford JD, Freeman AG. Thyroid Refractoriness in an Athyreotic Cretin Fed Soybean Formula. N Engl J Med. (1965) 273:83-7. doi: 10.1056/NEJM196507082730205.
29. Chorazy PA, Himelhoch S, Hopwood NJ, Greger NG, Postellon DC. Persistent hypothyroidism in an infant receiving a soy formula: case report and review of the literature. Pediatrics. (1995) 96(1 Pt 1):148-50.
30. Fruzza AG, Demeterco-Berggren C, Jones KL. Unawareness of the effects of soy intake on the management of congenital hypothyroidism. Pediatrics. (2012) 130(3):e699-702. doi: 10.1542/peds.2011-3350.

31. Conrad SC, Chiu H, Silverman BL. Soy formula complicates management of congenital hypothyroidism. Arch Dis Child. (2004) 89(1):37-40. doi: 10.1136/adc.2002.009365.
32. Wiesner A, Gajewska D, Paśko P. Levothyroxine Interactions with Food and Dietary Supplements-A Systematic Review. Pharmaceuticals (Basel). (2021) 14(3):206. doi: 10.3390/ph14030206.

Figure 1. Ultrasound of the thyroid gland showing the absence of thyroid tissue

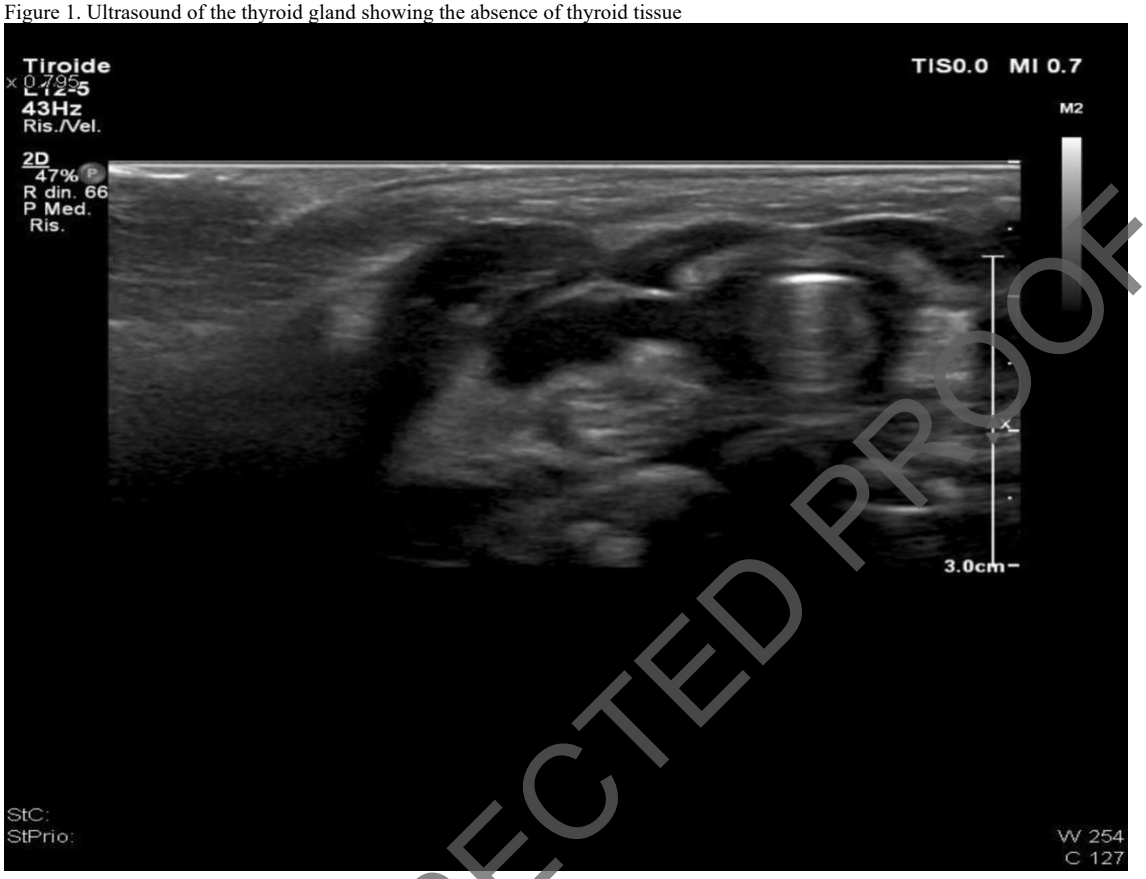

Figure 2. Trend in FT_4 and TSH, illustrating the effect of anti-reflux formula on their values.
FT_4: free T_4; TSH: thyroid-stimulating hormone