Unawareness of the Effects of Soy Intake on the Management of Congenital Hypothyroidism

abstract

It has been established that soy products can interfere with thyroid hormone absorption resulting in continued hypothyroidism in individuals receiving recommended levothyroxine replacement. It has also been reported that achievement of euthyroidism in hypothyroid patients using soy products requires increased doses of levothyroxine. We have observed 2 patients with congenital hypothyroidism who continued to manifest clinical hypothyroidism while receiving recommended doses of hormone and ingesting soy products. The first patient was diagnosed by newborn screening (thyroid-stimulating hormone [TSH] = 169 μIU/mL) and treated with 50 μg of levothyroxine since 6 days of age while simultaneously starting soy formula. At 3 weeks of age, she was clinically and biochemically hypothyroid (thyroxine = 4.0 μg/dL, TSH = 216 μIU/mL). We stopped her soy formula and decreased her levothyroxine dose. Three weeks later signs of hypothyroidism were resolving, and, by 10 weeks of age, she was clinically and biochemically euthyroid.

Another patient was diagnosed by newborn screening, received levothyroxine, and did well. She was lost to us for 2 years. During this interval she began consuming soy milk and became profoundly hypothyroid (free thyroxine <0.4 ng/dL, TSH = 248 μIU/mL), even though the primary care physician had increased her levothyroxine dose to 112 μg/day. She was switched to cow milk, and her thyroid function slowly normalized with decreasing doses of levothyroxine. These 2 patients reinforce the importance of remembering that soy products interfere with levothyroxine absorption and can endanger infants and young children with congenital hypothyroidism who are at risk for developmental and growth delay.
The first documentation of a goitrogenic effect of soy occurred in the 1930s with the development of goiters in rats fed raw soybeans. This was followed by soy-induced goiter in humans a quarter of a century later. In 1959, Van Wyk et al described an infant who had been fed a soy-based formula beginning shortly after birth and presented at 10 months of age with “cretinism” and a goiter. After discontinuation of this formula, the goiter and features of hypothyroidism disappeared, and the infant’s growth rate recovered a normal track. The authors mentioned that, while preparing their manuscript, they had become aware of an additional 8 cases of soy-related goiter with hypothyroidism. Another publication in 1960 describing a goiter in an otherwise euthyroid 5-month-old infant receiving soy formula confirmed this association. The introduction of iodine-supplemented soy formulas in the 1960s appeared to correct the problem without additional publications of soy-induced goiters in infants until 1995, when Chorazy et al reported the persistence of hypothyroidism in an infant with congenital hypothyroidism (CH) taking a soy-based formula while receiving levothyroxine doses as high as 14.5 μg/kg per day.

Notwithstanding the long history of this known effect of soy formulas with hypothyroidism and warnings in levothyroxine package inserts, errors with this combination persist. We have recently observed 2 patients with diagnoses of CH and persistent hypothyroidism while they were receiving recommended levothyroxine dosing and soy feeding. The hypothyroidism of 1 patient was not corrected with recommended levothyroxine replacement, and hypothyroidism redeveloped in the second patient after the introduction of soy-based products.

**Patient 1**

This infant girl was initially seen at 3 weeks of age; she had been diagnosed with CH by newborn screening with blood spot on filter paper (thyroid-stimulating hormone [TSH] =167 μIU/mL). At 6 days of age she began therapy with 50 μg (15 μg/kg birth weight) of levothyroxine. She was also fed with a soy-based formula, started because of a diagnosis of lactose intolerance in an older brother. She consumed 2 ounces of ProSobee soy milk every 2 hours, and levothyroxine was administered 1 hour after each feed. Medication compliance was excellent, but when she was seen for reevaluation by her primary care physician, she was hypotonic and had lost weight. Repeat thyroid function studies demonstrated a thyroxine (T4) level of 2.6 μg/dL (normal, 11–21.5 μg/dL) and a TSH level of 248 μIU/mL (normal, 1–20 μIU/mL) and she was referred to Rady Children’s Hospital San Diego Pediatric Endocrinology. Examination revealed a 3.4 kg (19th percentile) hypotonic infant with mild icterus. She had a hoarse cry, dry skin, and delayed relaxation of deep tendon reflexes. Her mother said that she cried less than her older brother had at her age and frequently had to be awakened to feed. Her suck was not vigorous. A neck ultrasound at 3 weeks of age did not show any thyroid tissue within the thyroid bed. The soy formula was discontinued and levothyroxine continued. Within the first week the mother called to report that the baby was more alert, feeding better, and that her cry was more normal. The results of her examination 3 weeks later were normal and have remained so, with her meeting normal developmental milestones and weight at the 42nd percentile. Thyroid function studies are shown in Fig 1.

**Patient 2**

This 5-year-old girl was diagnosed with CH by newborn screening with blood spot on filter paper: A nuclear medicine thyroid uptake scan and neck ultrasound were consistent with thyroid agenesis. She was started on levothyroxine therapy and initially did well, but she was lost to our clinic for 2 years, finally returning at age 5 years. During this interval, her diet was changed, so that she was given 8 oz of Silk soy milk daily rather than cow milk. On most occasions, her levothyroxine administration was at least 1 hour after soy intake. Her stature dropped from the 25th to the 9th percentile, and she became profoundly clinically hypothyroid. Testing at her return to our care revealed a free T4 <0.4 ng/dL (normal, 0.71–1.85 ng/dL) and a TSH level of 248 μIU/mL. This situation had developed even though her primary care physician had gradually increased her levothyroxine dose from 37.5 μg/day (11.5 μg/kg per day). At presentation to us, she was clinically hypothyroid, constipated, and unable to identify letters or numbers. When her diet was changed to include cow milk and soy milk was discontinued, her TSH level improved to 1.48 μIU/mL, and her T4 level increased to 18 μg/dL. During this time, her weight decreased from the 55th to the 34th percentile. Her levothyroxine dose was decreased to 100 μg daily (5 μg/kg per day), and, 4 weeks later, her total T4 normalized to 11 μg/dL, but her TSH remained suppressed at < 0.03 μIU/mL. Her levothyroxine was further decreased to 75 μg/day (4 μg/kg per day) with normalization of her thyroid function. Thyroid function studies are shown in Fig 2.

**DISCUSSION**

As briefly reviewed above, the potential thyroid consequences of ingesting soybean products and soy proteins have been documented for decades. In vitro studies suggest that phytoestrogens affect T3 and T4 synthesis by inhibiting thyroid peroxidase. The impact in healthy individuals and those with hypothyroidism has been extensively reviewed by Messina and Redmond. They emphasize that the major impact of soy
products and the isoflavones they contain is their effect on normal thyroid function and interference with the absorption of administered thyroid hormone in individuals with hypothyroidism. In their meta-analysis of 14 studies, none of which had thyroid function as a primary outcome, they concluded that there were no clinically significant adverse effects on thyroid function in healthy adults, and the levothyroxine dose might need to be increased in hypothyroid adults on replacement therapy. The exception, they point out, may be in infants with CH. A recent study of administration of soy phytoestrogen in 2 different doses to individuals with subclinical hypothyroidism found that 10% of the 60 subjects progressed to overt hypothyroidism while receiving 16 mg/day over 8 weeks. This dose was selected to duplicate the amount of phytoestrogen in a vegetarian diet.

After the observation by Van Wyk et al., Pinchera et al. reported an infant with CH who was receiving replacement with a desiccated thyroid preparation and became hypothyroid after switching from whole milk to a soy-based formula. The infant described by Chorazy et al. resembles our Patient 1. The infant described was placed on a soy-based formula because of intolerance of milk by an older sibling. A slightly different perspective of the same soy effect was provided by the observation of 2 infants who required a decrease in their levothyroxine replacement after moving from soy formula to milk and a third who maintained elevated TSH measurements in the face of large doses of levothyroxine (19 μg/kg per day) and required a reduction in replacement when soy formula was discontinued.

The course of the second child described makes the point that we must pay attention not only to hypothyroid infants, but also to all hypothyroid children. This 5-year-old girl was receiving a very large levothyroxine dose and was still clinically and biochemically hypothyroid with slowing of her growth. We do not know if still larger doses would have improved her hypothyroidism, but discontinuing soy milk corrected it and required a reduction to more normal dosing to achieve euthyroidism.

To evaluate the effect of soy formula feeding on infant thyroid function, Conrad and colleagues reviewed 78 infants with CH. By the time the first TSH was measured on therapy, the median TSH level was a significantly lower in infants receiving standard infant formula compared with soy-based formula. By 4 months of age, a higher percentage of the infants receiving soy-based formula still had a TSH > 10 mIU/L in comparison with infants receiving standard infant formula. The authors concluded that infants with CH who were fed soy formula needed close monitoring of T4 and TSH and might also need higher doses of thyroxine to achieve TSH normalization. The proposed mechanism to explain the prolonged increase of TSH in this study is through malabsorption and increased fecal loss of levothyroxine. Although this study was criticized for differences in sample size and variation in TSH measurement, its conclusions are consistent with the other observations cited.
According to the American Pediatrics Committee on Nutrition, there are few indications for use of soy-based formulas in place of cow milk–based formula. These indications are limited to (1) infants with galactosemia and hereditary lactase deficiency (rare) and (2) situations in which a vegetarian diet is preferred. Isolated soy protein–based formula has no advantage over cow milk protein–based formula as a supplement for the breastfed infant, unless the infant has one of the indications noted previously. Furthermore, the routine use of isolated soy protein–based formula has no proven value in the prevention or management of infantile colic, fussiness, or atopic disease. It is also worth mentioning that neither of the patients reported here required the soy products they received.

**CONCLUSIONS**

We have seen and treated 2 patients with CH who experienced either persistent or recurrent hypothyroidism while receiving soy products and recommended levothyroxine dosing. Although this is a well-documented phenomenon, it appears to have slipped from the universal knowledge base. Package inserts for preparations of oral levothyroxine do contain warnings about the effects of soy products. Based on our experience, we would make the following recommendations for children requiring levothyroxine replacement. Avoid the use of soy products unless necessary. If soy products must be used, carefully monitor thyroid function and use the dose necessary to maintain euthyroid T4 and TSH, even though it may be higher than usual recommended dosage. If soy products are discontinued in someone receiving levothyroxine replacement, monitor thyroid function to avoid iatrogenic hyperthyroidism.

**REFERENCES**

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