Case report

Improvement in metabolic indices including thyroid hormones via enhanced absorption of nutrients by Teduglutide in short bowel syndrome

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\textbf{ABSTRACT}

\textbf{Introduction and importance:} Short bowel syndrome is characterized by maldigestion and malabsorption resulting in deficiencies of multiple nutrients including vitamins and minerals. Most subjects required parental elimination for survival. GLP-2 RA Teduglutide was recently approved for treatment of short bowel syndrome especially for those requiring parenteral support. Our intent in reporting this subject is to demonstrate the utility of Teduglutide in improving multiple metabolic indices in presence of short bowel syndrome.

\textbf{Case presentation and clinical discussion:} 66-year-old Caucasian female presented with a history of short bowel syndrome and associated vitamin deficiencies, hypothyroidism requiring large dose (300 \textmu g) of levothyroxine, diarrhea and liver cirrhosis. Upon starting teduglutide the subject saw improvement in her symptoms. Moreover, daily dose of Levothyroxine required a gradual decrease to maintain desirable serum concentrations of Free T4, Free T3 and TSH. Serum levels of several vitamins attained greater than therapeutic concentrations requiring dosage reductions. Also notable was the improvement in her liver function tests, remission from ascites and episodes of hepatic encephalopathy and regeneration of liver nodules.

\textbf{Conclusion:} Following administration of GLP2 therapy, an adult subject with short bowel syndrome with concurrent hypothyroidism and multiple vitamin deficiencies, demonstrated a marked improvement in her metabolic parameters resulting in reduction in daily medication doses along with improvement in manifestations of liver cirrhosis.

1. Introduction

Subcutaneous Teduglutide is an analog of glucagon-like peptide 2 (GLP-2) which regulates growth, proliferation and maintenance of cells lining the gastrointestinal tract \cite{1–3}. Teduglutide has been approved for the treatment of patients with short bowel syndrome (SBS) who need parenteral support \cite{1}. Short bowel syndrome is the consequence of a loss of bowel mass due to extensive surgical resection, congenital defects or other rare disorders \cite{4,5}. Teduglutide improves intestinal rehabilitation by promoting mucosal growth and possibly by inhibiting gastric emptying and secretion which in turn reduces intestinal losses and promotes intestinal absorption \cite{1,2}. Most studies have focused on the utility of teduglutide on reducing the need for parenteral support for patients with SBS-Intestinal failure \cite{3,6,7}. We report an adult subject with short bowel syndrome with consequential hepatic cirrhosis with several episodes of encephalopathy and concurrent hypothyroidism as well as multiple nutritional and vitamin deficiencies. Administration of Teduglutide normalized metabolic abnormalities, requiring reduction or discontinuation in daily dose of multiple nutritional supplements, along with normalization of liver function tests and remission from hepatic cirrhosis, ascites and hepatic encephalopathy.

2. Case report

66-year-old female was referred to endocrinology clinic because her serum TSH concentration remained elevated despite appropriate administration of levothyroxine over 250 \textmu g (2.8 \textmu g/kg body weight) taken daily by itself in the morning on an empty stomach with water approximately 1 h prior to breakfast. On further inquiry, she reported a history of short bowel syndrome, a sequela resulting from an extensive

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Persistent Improvement in Metabolic Abnormalities over 3 year period following administration of Teduglutide.

|        | Normal range | Aug 18 | Jan 19 | Jun 19 | Dec 19 | Apr 20 | Nov 20 | Feb 21 | Dec 21 |
|--------|--------------|--------|--------|--------|--------|--------|--------|--------|--------|
| Free T4| 0.89–1.76 ng/dl | 1.53   | 1.68   | 1.21   | 1.22   | 1.16   | 1.53   | 1.48   |
| TSH    | 0.55–4.78 mIU/ml | 0.286 | 0.011  | 4.318  | 3.343  | 2.561  | 3.969  | 3.228  |
| Calcium| 8.7–10.4 mg/dl | 9.7    | 9      | 9.5    | 10     | 9.4    | 9.3    | 8.9    |
| Vitamin D| 30–80 ng/ml | 20.1   | 20.1   | 20.1   | 20.1   | 20.1   | 20.1   | 20.1   |
| Vitamin A| 32.5–78 μg/dl | 42.7   | 42.7   | 42.7   | 42.7   | 42.7   | 42.7   | 42.7   |
| Iron   | 50–175 mg/dL | 68     | 74     | 45     | 390    | 273    | >2000  | >2000  |
| Vitamin E| 5.5–17 mg/L | 23     | 29     | 29     | 28     | 21     | 18     |
| Vitamin B12| 211–911 μg/ml | 390   | 273    | >2000  | >2000  | >2000  | >2000  |
| INR    | 0.9–1.1 ratio | 1.1    | 1.1    | 1.1    | 1.1    | 1.1    | 1.1    |
| TIBC   | 250–450 μg/dl | 252    | 297    | 319    | 298    | 323    | 272    |
| Ferritin | 0–291 ng/ml | 640    | 569    | 517    | 760.7  | 861.3  | 823.3  |
| AST    | 0–37 IU/L    | 26     | 31     | 32     | 21     | 31     | 31     |
| ALT    | 10–49 IU/L   | 27     | 37     | 44     | 24     | 37     | 41     |
| Alkaline phosphatase | 45–129 IU/L | 76     | 88     | 108    | 93     | 87     | 71     |
| Ammonia| 11–35 μmol/L | 13     | 32     | 24     | 18     | 34     |
| Alpha Fetoprotein | <8.1 ng/ml | 10.3   | 8.8    | 7.4    | 8.3    | 5.2    |

3. Discussion

Short bowel syndrome is characterized by an “inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventional, normal diet.” [5]. A subset of these patients have “intestinal failure” resulting in deficiency of multiple vitamins and minerals induced by malabsorption and malnutrition [5]. Intermittent parenteral hyperalimentation has been the mainstay to meet daily nutritional needs. However, painstaking attempts are also undertaken to administer orally mega doses of fat soluble vitamins to attain and maintain normal concentrations with some success [4,5]. In patients receiving parenteral nutrition vitamin D still needs to be replaced orally due to lack of availability of IV formulation [4,5].

Glucagon-like peptide 2 (GLP-2) is a gastrointestinal peptide secreted by L-cells of the intestinal mucosa in response to luminal contact with unabsorbed nutrients. It promotes mucosal growth, enhances release of intestinal enzymes and delays gastric transit time to promote absorption of nutrients by slowing entry of food into the short bowel [1,2].

Teduglutide, an analog of GLP 2, is approved as the first long-term medical therapy for treatment of adults with SBS dependent on...
parenteral support [1]. Teduglutide has been shown to be safe and well-tolerated by patients. It promotes “restoration of structural and functional integrity of the remaining intestine with significant intestino-trrophic and pro-absorptive effects, facilitating a reduction in diarrhea as well as frequency of parenteral support in patients with SBS and consequential ‘intestinal failure’” [1,4,5].

Hepatocellular injury has been documented in patients with short bowel syndrome/intestinal failure and is attributed to lack of nutrient supply to liver by decrease in nutrients in the spared gut due to malabsorption [9,10]. Long-term parenteral support has been thought to delay onset of liver disorder by supplementation of nutrients directly to the liver through systemic circulation [3,5,8]. A recent study suggests that liver damage ensues as a “consequence of the disrupted enterohepatic circulation following intestinal resection, leading to biliary hypersecretion, bile acid dysmetabolism, and microbial dysbiosis” [11].

Apparently, this is the first report of reversal of cirrhosis with administration of teduglutide as evidenced by remission from hepatic encephalopathy, ascites and normalization of liver enzymes. This finding is consistent with a recent study which showed that low dose GLP-2 administration improves hepatic steatosis in parenterally fed rat model of short bowel syndrome [9]. Reversal in hepatic steatosis is attributed to increased splanchnic blood flow and improvement in cholestasis [11,12]. We attribute reversal of cirrhosis and its complications in our patient to the transport to the liver via portal vein of nutrients in the intestinal lumen induced by enhanced digestion and absorption of ingested food on administration of Teduglutide.

The work is reported in line with the SCARE criteria [13].

Table 2

| Requirement for dose reduction or discontinuation for several dietary supplements over 3 year period following administration of Teduglutide. |
|---|---|---|---|---|---|---|---|---|
| **Dye** | **August 2018** | **January 2019** | **June 2019** | **December 2019** | **April 2020** | **November 2020** | **February 2021** | **December 2021** |
| Vitamin D | 50,000 units weekly | 50,000 units weekly | 50,000 units weekly | 50,000 units weekly | 50,000 units weekly | 50,000 units weekly | 50,000 units every 2 weeks | 50,000 units every 2 weeks |
| Vitamin A | 8000 units Daily | 8000 units Daily | 8000 units Daily | Discontinued | Discontinued | Discontinued | Discontinued | Discontinued |
| Levothyroxine | 250 μg Daily | 150 μg Daily | 150 μg Daily | 150 μg Daily | 150 μg Daily | 150 μg Daily | 150 μg Daily | 150 μg Daily |
| Vitamin E | 1000 units Daily | 1000 units QOD days | 1000 units Q 3 days | Discontinued | Discontinued | Discontinued | Discontinued | Discontinued |
| Vitamin B12 | 1000 units Monthly | 1000 units Monthly | 1000 units Monthly | Discontinued | Discontinued | Discontinued | Discontinued | Discontinued |
| Iron | 300 mg IV Monthly | 300 mg IV Monthly | 300 mg IV Monthly | 300 mg IV Monthly | 300 mg IV Monthly | 300 mg IV Monthly | 300 mg IV Monthly | 150 mg IV Monthly |
| Lactulose | 550 mg BID Discontinued | 550 mg BID Discontinued | 550 mg BID Discontinued | 550 mg BID Discontinued | 550 mg BID Discontinued | 550 mg BID Discontinued | 550 mg BID Discontinued | 550 mg BID Discontinued |

Guarantor

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CRediT authorship contribution statement

All three authors contributed to management of the patient and contributed in preparation of manuscript.

Declaration of competing interest

None.

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