ECHO Diabetes
Short Bowel Syndrome & Diabetes

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Selecting Medication/Treatments for Diabetes

- Efficacy (how well they lower the blood glucose)
  - “Therapeutic Heterogeneity” – not everything works the same for everyone
  - “Precision Medicine” – matching treatments to the individual’s genetic makeup and other characteristics
- Benefits vs Risks/Harms
  - Added benefits such as reducing CVD risk, preserving renal function, preventing HF, reversing fatty liver/MASLD, weight reduction
    - The ADA, EASD, American College of Physicians T2D guidelines recommend choosing a medication that offers additional benefits beyond just glucose lowering over one that only reduces glucose
  - Effects on co-existing conditions
    - Heart failure/fluid balance (SGLT2i meds improve; TZD meds worsen)
    - Osteoporosis (increased fracture risk with TZD)
    - Liver disease (reduced Hepato-Cellular Carcinoma (HCC) with metformin, improved MASLD with GLP1 RA and pioglitazone and ~ SGLT2i))
    - Gallbladder issues (caution with GLP1 RA meds)
    - Gout (reduced by SGLT2i meds)
    - Other – Short Bowel Syndrome

Short Bowel Syndrome (SBS)

- **Short bowel syndrome (SBS) occurs when part of the small intestine is missing or isn't working properly**.
  - It can be present from birth or develop after surgery to remove a large section of the small intestine (usually more than two thirds of its length).
  - This can lead to ***poor absorption of nutrients and fluids (malabsorption)*** *causing* ***diarrhea and malnutrition***.
- People with short bowel syndrome may have:
  - **Gas**
  - **Cramps**
  - **Diarrhea (loose or watery stools)**
  - **Fluid Loss**
  - **Weight loss**
  - **Nausea**

SBS continued

- Common reasons for removing a large portion of small intestine in adults are:
  - Crohn disease – 10 to 20%
  - a blockage of an artery that supplies blood to a large part of the intestine (**mesenteric infarction**) – 25 to 30%
  - surgical complications -29 to 50%
  - inflammation of the intestine caused by radiation (radiation enteritis) – 10%
  - Cancer – 20%
  - a twisted loop of intestine (volvulus)
- The Small Intestine
  - Most digestion and absorption of food takes place in the small intestine. The small intestine is about 12 to 21 feet (about 4 meters) in length.
  - The consequences of removing a portion of the small intestine depend on how much is removed and its location.
    - If the middle part (jejunum) is removed, sometimes the last part (ileum) can adapt and absorb more nutrients.
    - If more than about 3 feet (about 1 meter) of ileum is removed, the remaining small intestine usually cannot adapt (Intestinal Failure).
      - Before adaptation occurs, or if it does not, the intestines have difficulty absorbing many nutrients, including fats, proteins, and vitamins.
    - If the end of the ileum has been removed, the intestines also cannot absorb bile acids secreted by the liver, which aid digestion and cannot absorb vitamin B12. The excess bile acids enter the colon and can cause diarrhea.
  - Malabsorption causes ***diarrhea***, typically beginning immediately after the surgery. Later, people develop ***undernutrition*** and ***vitamin deficiencies***, such as B12 deficiency.

Treatment of Short Bowel Syndrome

- **Total parenteral nutrition (TPN)**
  - Immediately after surgery, when diarrhea is typically severe, doctors give intravenous fluids to replace fluid and electrolyte losses and usually also give intravenous feedings.
    - These feedings, called ***total parenteral nutrition (TPN),*** contain all necessary nutrients, including proteins, fats, carbohydrates, vitamins, and minerals.
    - As people recover and their stool output lessens, they are slowly given fluids by mouth.
  - People who have had a large amount of small intestine removed (such as those with less than 3 feet [about 1 meter] of remaining small intestine) and those who continue to have excessive fluid and other nutrient losses ***require TPN for life***.
  - People 1 year of age and older who need TPN may be given injections of a medication called ***teduglutide (a GLP2 analog)***. This medication may help reduce the amount of TPN people need.
    - Helps improve absorption by remaining small intestine

Treatment of Short Bowel Syndrome

- **Antidiarrheal medications, nutritional supplements & proton pump inhibitors**
  - If people tolerate food by mouth, ***small, frequent meals*** are better than fewer, large ones.
  - People with short bowel syndrome (SBS) may benefit from a diet that includes:
    - Complex carbohydrates (the best type of carbohydrates for people with SBS)
      - but limit high insoluble fiber snacks like popcorn
    - Avoid sweets as much as possible – they increase diarrhea
    - Protein: High-quality protein from foods like meat, poultry, fish, and eggs is important.
    - Sodium supplementation: People with SBS may be at risk of losing too much sodium.
    - Low-oxalate diet: If the colon is intact - may need to limit foods that are high in oxalate, which can cause kidney stones. (high oxalate foods include cocoa, peanut products, tea, coffee, wheat germ, rhubarb, beets, collards, spinach, tofu, and soybeans)
    - Avoiding FODMAPs (carbohydrates and sugar alcohols that are poorly absorbed in the small intestine)
    - More complete diet recommendations in extra slide section
  - People who have diarrhea after meals can take antidiarrheal medications such as loperamide 1 hour before eating.
    - Cholestyramine can be taken with meals to reduce diarrhea caused by malabsorption of bile acid.
  - Most people should ***take supplemental vitamins, calcium, and magnesium***.
  - Some people require monthly injections of vitamin B12.
  - Because people with short bowel syndrome often have ***excess stomach acid***, most people also take an acid-blocking medication, such as a proton pump inhibitor.

Dietary Recommendations for SBS

- Eat 6 to 8 small meals a day
  - Eat small, frequent meals to put less stress on your shortened bowel. Small meals help control your symptoms and are easier for your body to digest and absorb.
  - Eat slowly and chew your food well.
  - Once your bowel has adapted, you can go back to having 3 meals a day.
- Chew foods well
  - Chew foods well to help break down food and makes it ***easier for your body to absorb***.
  - It will also help ***stop foods from causing a blockage*** as they pass through your intestine.
- Only drink ½ cup (4 ounces) of liquids during each meal
  - Drink most of your liquids between meals, at least 1 hour before or after a meal.
  - Drinking large amounts of liquids with meals helps push food through the bowel more quickly. This means that you may not digest or absorb enough nutrients.
- Include enough liquids in your diet
  - Drink at least 8 (8-ounce) glasses of liquids each day.
  - Avoid very hot or vey cold drinks.
  - Choose ***drinks that don't have a lot of sugar***. This will keep you from getting dehydrated. Examples include water, coffee, tea, milk, or juices diluted with water.
  - Be careful, ***coffee may have a laxative effect*** on some people.

For treating SBS meals should be

- ***High in refined or low-fiber complex carbohydrates (starches).*** Examples include:
  - White bread
  - Cereals such as Rice Krispies® and corn flakes
  - Potatoes without skin
  - White rice
  - White pastas

For Complex carbs focus on Soluble fiber vs insoluble fiber

- ***Low in sugary foods***. Examples of sugary foods are:
  - Sugar (cookies, cakes, candies, chocolate, soda, instant teas, fruit drinks)
  - Corn syrup
  - Molasses
  - Honey
  - Pancake syrup
  - You can use artificial sweeteners like Splenda® or Sweet N' Low®.
  - However, **limit your intake** of sugar-free candies or cough drops that contain **sugar alcohols**. Sugar alcohols ***include sorbitol, xylitol, mannitol, and isomalt***. Having large amounts of these may have a ***laxative effect*** (make you have a bowel movement).

Candy, fruit juices and sodas that are high in simple sugars, pull water into the gastrointestinal (GI) tract and lead to fluid and nutrient loss

For treating SBS meals should be

- ***High in proteins***. Examples of protein-rich foods include:
  - Fish
  - Eggs
  - Tofu
  - Poultry, such as chicken and turkey
  - Meat, such as beef, pork, and lamb
  - Dairy products, such as milk, cheese, and yogurt
  - Smooth peanut butter and other nut butters, such as almond butter
- ***Moderate in fats***. Examples of fatty foods are:
  - Oils Butter
  - Margarine
  - Mayonnaise
  - Gravies
  - Cream sauces
  - Gravies
  - Cream sauces
  - Regular salad dressings
  - For example, it's okay to have butter on toast or mayonnaise on a sandwich. But, it's better to ***avoid very high-fat foods, such as deep-fried foods.***
  - If a large section of your ileum was removed, you may tolerate fats better at breakfast than later in the day.

How does SBS affect Diabetes?

- Hypomagnesemia
  - Hypomagnesemia can increase insulin resistance and reduce the activity of pancreatic β-cells (less insulin secretion) in people with T2D.
  - Chronic hypomagnesemia can lead to the development of macro and microvascular complications of diabetes.
- Hypokalemia
  - Hypokalemia can cause the pancreas to release less insulin, leading to higher blood sugar levels & lead to impaired glucose tolerance & more likely to develop type 2 diabetes.
  - Higher risk of atrial fibrillation, respiratory muscle impairment, Q-T interval increase, torsade des pointes, and ventricular fibrillation, and ***higher morbidity and mortality*** in diabetic individuals especially with HF & CKD Hypokalemia in Diabetes Mellitus Setting - PMC (nih.gov)
- Reduced incretins
  - There are two main incretin hormones in humans: GIP (glucose-dependent insulinotropic peptide; also known as gastric inhibitory peptide) and GLP-1 (glucagon-like peptide-1).
    - Incretins have a number of important biological effects on the pancreas, including **the release of insulin and maintenance of β-cell mass.**
    - Both hormones are secreted by endocrine cells that are located in the epithelium of the **small intestine**.
  - Massive small bowel resection is associated with **hepatic steatosis, abnormal body composition (more fat, less lean), and impaired glucose metabolism, persistent hyperglycemia**, but without insulin resistance – lower GLP1 levels and reduced beta cell function

The Efficacy of the GLP-1 Agonist Exenatide in the Treatment of Short Bowel Syndrome. Pimentel, Mark MD; et al

American Journal of Gastroenterology 102():p S201-S202, September 2007.

- Purpose: Short bowel syndrome (SBS) is a serious medical problem resulting in severe diarrhea and nutritional deprivation. The symptoms result from lack of absorptive surface and loss of the braking mechanisms controlling the proximal gut**. One of the missing, distally produced, peptides that control the proximal gut is glucagon-like peptide-1 (GLP-1). In this study we test the effect of the GLP-1 receptor agonist, exenatide, on short bowel syndrome**.
- Methods: SBS subjects were selected based on clinical symptoms and greater than 50% distal small bowel resection. Before beginning exenatide treatment, each patient completed a questionnaire documenting stool frequency and consistency. In addition, SBS symptoms, CBC, chemistries and BMI were also obtained. An antroduodenal manometry study was performed during fasting, after exenatide, and after a subsequent test meal. Each patient was then started on exenatide 5 to 10 mcg subcutaneously twice a day. Over the following month the baseline parameters measured were repeated.
- Results: The subjects consisted of 4 males and 1 female, ages 46 to 69 (mean: 57.2). At baseline, all patients had severe diarrhea that ranged from 7 to 15 bowel movements per day, often occurring within 15 minutes of eating. **After exenatide, all 5 patients had an immediate improvement in bowel frequency and form**. In the most severely affected patient, the bowel movements reduced from 15 watery bowel movements per day to 2–3 formed stool. In all subjects, bowel movements were no longer meal related and often occurred hours after any meal. At baseline nutritional parameters were stable due to total parenteral nutrition (TPN) in most cases (N = 3). **However, after exenatide, all 3 patients no longer needed TPN. Despite the lack of TPN, no weight loss or biochemical nutritional deterioration was observed in any case.** Previous attempts at ceasing TPN had resulted in immediate and life-threatening dehydraton and malnutrition. Using normal bowel function as a goal, subjects described their improvement with exenatide as 65–100% improved. Antroduodenal manometry in 2 out of 5 subjects demonstrated continuous low amplitude gastric contractions during fasting which completely normalized after exenatide.
- **Conclusion: Exenatide is a novel and safe treatment option for SBS. It normalizes bowel function and maintains nutritional status. Successful treatment with exenatide may significantly reduce the need for parenteral nutrition**.

A patient on parenteral nutrition: the problem of insulin therapy and more

Clin Diabetol 2021; 10; 3: 310–315

- Case: 46–year-old male with pre-existing diabetes
  - Acute Mesenteric Infarction due to thrombo-embolism associated with atrial fibrillation → Large section of small intestine removed – only ~ 20 inches remaining
  - Review issues with diabetes management associated with SBS & TPN
    - To help manage the SBS: "In patients with SBS, early treatment including GLP-2 analogues should be initiated as these drugs may restore normal intestinal absorption which allows partial return to oral food intake and administration of oral medications"
    - To help manage the diabetes in a patient with SBS: Require insulin with TPN
    - *"Due to incretin axis disruption following intestinal resection, initiation of incretin-based treatment should be considered, including with glucagon-like peptide 1 (GLP-1)."*
    - *"Patients with **SBS and concomitant diabetes** may potentially gain more benefits from the use of GLP-1 analogues"*

Considerations for GLP1 RA medications in PWD & SBS

- Improved SBS effects & symptoms
- Improved glycemia with less risk of hypoglycemia –
  - Effective & safe in CKD (reduced eGFR) & guidelines recommend for PWD & CKD
  - Replacing a missing incretin (GLP1) –
  - Would dual agonist therapy (tirzepatide) provide better replacement of what is missing & effect (both GIP & GLP1)??? [in T2D - studies show greater glycemic benefit (lower A1c)]
    - Could not find reports specific to SBS
- What about N&V? - What is causing the patient's N&V currently?
  - SBS – N&V should improve with improvement in SBS symptoms with GLP1 RA
    - Would dual agonist therapy (tirzepatide) reduce risk of side effect of nausea
    - Preclinical studies suggest that GIP has an anti-nausea effect. GIPRAs may reduce GLP-1RA-induced nausea and vomiting by activating a local inhibitory network in the caudal hindbrain https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8564411/
  - Cannabis use – Cannabis Hyperemesis Syndrome (CHS)
    - Prodromal phase: Nausea worse in morning ("morning sickness")
      - Normal eating patterns and use more weed to keep the nausea at bay
    - Hyperemetic phase: cyclic severe N&V x 24-48 hours
      - Relief with hot showers/baths – no relief with typical anti-emetics

Cannabis Hyperemesis Syndrome

- Symptoms of CHS typically come on several years after the start of chronic marijuana use. Common symptoms of cannabinoid hyperemesis syndrome include:
  - Persistent nausea — often in the morning.
  - Repeated vomiting and retching up to five times an hour.
  - Intense abdominal discomfort or pain.
  - Fear of throwing up.
  - Loss of appetite.
  - Hot baths and showers tend to help reduce or curb the symptoms. Many people with CHS will compulsively shower or bathe — often for hours every day — to relieve CHS symptoms.
  - One study found that spicy food, greasy food, coffee, black tea, and alcohol were frequently mentioned as CHS triggers.

- Symptoms of CHS and their severity depend on the phase of the syndrome:
  - Prodromal phase: This phase is most common in adults who have used cannabis since they were teenagers. May have abdominal pain or morning nausea - may also fear throwing up but never actually vomit. This phase can last for months or years.
  - Hyperemetic phase: This is the characteristic phase of CHS. It usually lasts 24 to 48 hours and involves overwhelming, recurrent vomiting and nausea - may start compulsively bathing and avoid certain foods or purposefully restrict food intake.
  - Recovery phase: During recovery, ***stop using cannabis (even in small amounts),*** symptoms lessen over a few days or months. Eventually, they completely disappear.

What about SGLT2i medications?

- Potential causes of electrolyte issues [low Magnesium (Mg++) & Potassium (K+)]
  - Decreased Magnesium absorption associated with SBS
    - Also, increased renal losses of Mg++
    - Hypomagnesemia can result in hypokalemia
  - Diarrhea – GI losses of both Mg++ & K+
    - (patient having constipation - ? Due to low Mg++ & K+)
  - Diabetes – vicious cycles with low Mg++ & low K+ ←→ hyperglycemia
  - PPI
  - Cannabis
  - Other
  - ? SGLT2i – was this worsening her electrolyte imbalance?
    - Modulates potassium – less high or low potassium levels https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4801817/
    - What about magnesium?

Hypomagnesemia in Type 2 Diabetes: A Vicious Circle?

Lisanne M.M. Gommers; Joost G.J. Hoenderop; René J.M. Bindels; Jeroen H.F. de Baaij

Diabetes 2016;65(1):3–13

- Over the past decades, hypomagnesemia (serum Mg2+ <1.7 mg/dl) has been strongly associated with type 2 diabetes mellitus (T2DM).
- T2DM patients with hypomagnesemia have **reduced pancreatic β-cell activity** and are **more insulin resistant**
  - suggesting that Mg2+ is an important factor in the etiology and management of T2DM
- Patients with hypomagnesemia show a **more rapid disease progression** and have an **increased risk for diabetes complications**.
  - Hypomagnesemia is associated with an increased risk for complications, including ***retinopathy, nephropathy, and foot ulcers***
  - Hypomagnesemia is associated with a ***more rapid, and permanent, decline in renal function*** in patients with T2DM

Hypomagnesemia in Type 2 Diabetes: A Vicious Circle?

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Diabetes 2016;65(1):3–13

- In T2DM, the prevalence of hypomagnesemia ranges between 14 and 48% compared with between 2.5 and 15% in healthy control subjects.
- Impaired intestinal Mg2+ absorption or renal Mg2+ wasting can lead to hypomagnesemia
  - Insulin excess (as in IR) can cause renal wasting of magnesium
  - Patients using widely prescribed drugs such as **thiazide diuretics, proton pump inhibitors, and calcineurin inhibitors** (e.g., tacrolimus) are especially at risk for developing hypomagnesemia
- Patients with T2DM and hypomagnesemia enter a ***vicious circle*** in which **hypomagnesemia causes insulin resistance and insulin resistance reduces serum Mg2+ concentrations**.

[A case of hypomagnesemia linked to refractory hypokalemia and hypocalcemia with short bowel syndrome]

[Article in Japanese] Yuki Sato et al, Nihon Jinzo Gakkai Shi. 2012;54(8):1197-202.

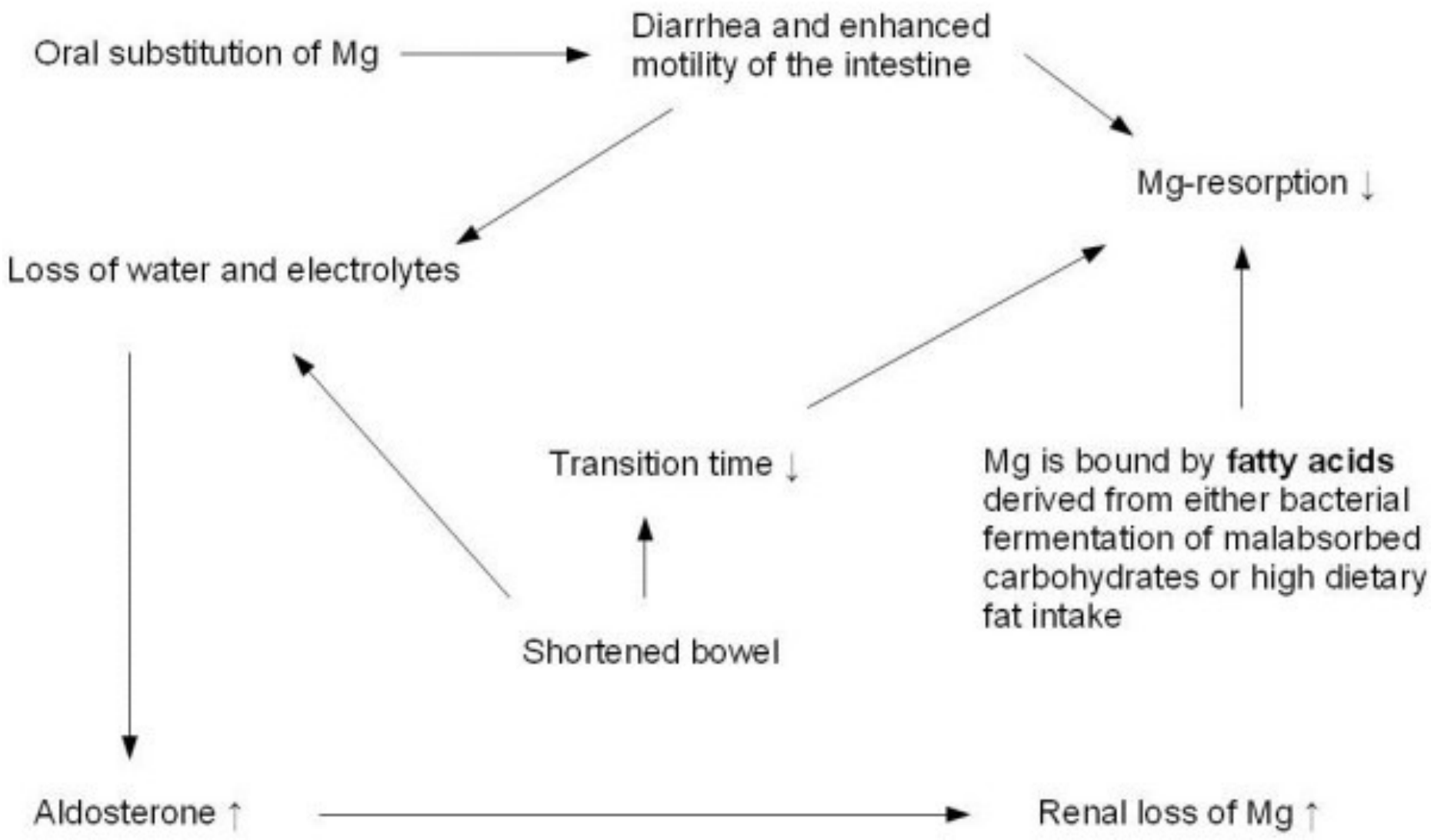
- Abstract: We report a case of a 59-year old Japanese woman with **short bowel syndrome, whose hypokalemia and hypocalcemia were successfully treated with magnesium (Mg) supplementation.**
- Two years previously, she underwent Mile's operation for advanced rectal cancer, which could have been the cause of subsequent extensive resection of the small intestine by strangulation. After serial resection, she gradually developed chronic diarrhea and anorexia. Three weeks before admission, she developed general fatigue and tetany, and was hospitalized at another hospital. On admission, her serum K and Ca were 2.5 mEq/L and 4.3 mg/dL, respectively, hence regular fluid therapy containing potassium (K) and calcium (Ca) was provided following admission. However, her hypokalemia and hypocalcemia persisted, and she also displayed renal dysfunction and thereafter was transferred to our department for further evaluation and treatment. Since the laboratory tests revealed severe hypomagnesemia (0.4 mg/dL), we started intravenous Mg supplementation together with fluid therapy containing K and Ca. After the combination therapy, her clinical symptoms and electrolyte disorders were remarkably improved within a week.
- As Mg is essential for PTH secretion in response to hypocalcemia and to inhibit the K channel activity that controls urinary K excretion, **hypomagnesemia can cause hypocalcemia and hypokalemia, which is refractory to repletion therapy unless Mg is administered**. Therefore, for patients who present with signs of Mg deficiency, early and accurate diagnosis of Mg deficiency should be made and corrected.

SGLT2 Inhibitors in Management of Severe Hypomagnesemia in Patients Without Diabetes: A Report of 4 Cases

Kidney Med. 2023 Sep; 5(9): 100697. Chintan V. Shah, Nour Hammad, Bhavna Bhasin-Chhabra, and Arash Rashidi

- Abstract: Sodium/glucose cotransporter 2 (SGLT2) inhibitors have demonstrated a **class effect in improving serum magnesium levels in patients with diabetes**.
- Additionally, recent reports have shown their promising **beneficial effects in the treatment of refractory hypomagnesemia in patients with diabetes.**
- However, their role in treating hypomagnesemia in patients without diabetes remains unexplored. Here, we report **4 cases of severe and refractory hypomagnesemia that showed dramatic improvement after initiating SGLT2 inhibitors in patients without diabetes.**
- Case 1 had calcineurin inhibitor-associated severe hypomagnesemia. Cases 2, 3, and 4 had refractory hypomagnesemia associated with platinum-based chemotherapy with or without gastrointestinal losses. Case 1 was able to withdraw from high-dose oral magnesium supplementation. Cases 2 and 3 achieved independence from intravenous magnesium supplementation, whereas case 4 had decreased intravenous magnesium requirements**.**
- **All the cases demonstrated sustainably improved serum magnesium levels**.
- **Withdrawal of SGLT2 inhibitors in case 4 resulted in worsening serum magnesium levels and intravenous magnesium requirements.**

Both GI & Renal Losses of Magnesium in SBS



Cannabis Use: An Uncommon Cause of Hypokalemia-Induced Acute Paralysis

Cureus. 2023 Aug; 15(8): e44393. Monitoring Editor: Alexander Muacevic and John R Adler
Angad Singh, Andre Apostolatos, Ajay Iyer, Benny Bescobedo, and Melissa Middlemas

- Abstract: Severe hypokalemia can have life-threatening complications such as significant muscle weakness, ileus, rhabdomyolysis, and respiratory failure.
- Here, we report a case of a 33-year-old male who presented with worsening lower extremity weakness and falls after smoking marijuana for six months.
  - Initial labs showed severe hypokalemia. EKG was remarkable for a first-degree AV block, widened QRS complex, and ST segment depression. Intravenous potassium replacement resulted in complete resolution of lower extremity motor weakness.
- Our case highlights the underdiagnosed association of **marijuana use with clinically significant hypokalemia** and the rare presentation of severe hypokalemia with acute paralysis.
- Cannabis-induced hypokalemia is thought to be due to a ***transcellular potassium shift*.**
  - Cannabinoids primarily exert many of their cellular and organ effects by activating the Gi/o protein-coupled, cannabinoid type 1 (CB1) and type 2 (CB2) receptors.

Summary of Considerations

- SBS can worsen diabetes due to reduced incretin levels, electrolyte imbalances &, in many cases, the use of TPN
- GLP1 RA or Dual agonist therapy is a good option
  - Replacing incretins that have been reduced by small intestine resection
  - Help SBS
  - Glycemic & non-glycemic benefits (renal, stroke, HFpEF)
- SGLT2i therapy could improve hypomagnesemia & hypokalemia (critical)
  - This should help glycemia & reduce risk complications, including sudden death
  - Additional glycemic & non-glycemic benefits (renal, HF)
  - Might exacerbate mycotic vaginal infections – emphasize preventive efforts
- Keep in mind that cannabis can cause N&V (CHS)
  - can increase anxiety
  - lead to hypokalemia

Extra Slides/References

Merlo FD, Aimasso U, Ossola M, Ippolito M, Cravero L, Ponzo V, Bo S. Effects of Treatment with Liraglutide Early after Surgical Intervention on Clinical Outcomes in Patients with Short Bowel Syndrome: A Pilot Observational "Real-Life" Study. Nutrients. 2023;15(12). doi: https://dx.doi.org/10.3390/nu15122740.

- Liraglutide, a glucagon-like peptide-1 agonist, has been shown to have beneficial effects on fecal output in short bowel syndrome (SBS) by small human studies. Its potential effects early after gut resection are not known. In this pilot observational study, we described the 1- and 6-month liraglutide effects in 19 adult patients with a new SBS diagnosis within 1 month after surgical resection. Stomal/fecal and urinary outcomes, serum/urinary electrolytes, and body composition were assessed. Both within-group differences and between-group comparisons with 20 SBS patients refusing liraglutide treatment were evaluated. The main liraglutide-related side effect was mild nausea, except in one patient, who experienced severe nausea/vomiting. The median ostomy/fecal output was significantly reduced by -550 mL/day after 6 months of treatment (vs. -200 mL/day in untreated, p = 0.04). The number of patients reaching a >=20% output reduction was 10/19 (52.6%) treated vs. 3/20 (15.0%) untreated patients (p = 0.013) at 1 month and 12/19 (63.2%) vs. 6/20 (30.0%) (p = 0.038) at 6 months, respectively. Participants with a clinically relevant output reduction at 6 months had a significantly lower baseline weight and BMI. Energy parenteral supply significantly decreased, while infused volumes, oral energy, and fluid intakes slightly decreased, though not significantly. This pilot study supports liraglutide benefits in ostomy/fecal output early after surgical gut resection in SBS patients, particularly in those with lower baseline weight values.

Conley TE, White KL, Bond A, Harrison S, McLaughlin J, Lal S. Emerging uses of glucagon-like peptide 1 (GLP-1) receptor agonists following ileal resection: Literature review and case examples. Frontline Gastroenterology. 2023;14(6):521-6. doi: https://dx.doi.org/10.1136/flgastro-2023-102402. PubMed PMID: 2025815273.

- Following ileal resection, the combination of severe bile acid (BA) malabsorption, rapid small bowel transit and unrestricted upper gastrointestinal (GI) secretion results in severe diarrhoea that can prove refractory to pharmacological therapies. While established therapies, including BA sequestrants and antidiarrhoeal drugs seek to ameliorate symptoms, they do not target the underlying pathophysiological mechanisms in this patient group. Their use can also be limited by both intolerance and adverse effects. The novel use of glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) in these patients may allow restoration of the physiological negative feedback mechanisms lost in ileal resection and reduce diarrhoea by prolonging small bowel transit time, limiting upper GI secretions and perhaps by inhibiting hepatic BA synthesis. While recent evidence supports the use of GLP-1 RAs as a safe and effective therapy for bile acid diarrhoea (BAD), it remains uncertain whether those with severe BAD and subsequent short bowel syndrome secondary to extensive ileal resection will benefit. Here, we present three cases of severe diarrhoea secondary to extensive ileal resection in which the use of the GLP-1 RA, liraglutide, was well tolerated and resulted in an objective improvement in diarrhoeal symptoms. We further provide a narrative review of the emerging evidence base supporting the use of GLP therapies in this challenging condition.

Verbiest A, Wauters L, Vanuytsel T. Enterohormone therapy for short bowel syndrome. Current opinion in endocrinology, diabetes, and obesity. 2022;29(2):207-18. doi: https://dx.doi.org/10.1097/MED.0000000000000710.

- PURPOSE OF REVIEW: Short bowel syndrome (SBS) patients are at risk to develop intestinal failure when the decreased absorption of macronutrients, water, and electrolytes necessitates parenteral support for survival. The adverse effects of SBS and parenteral support negatively affect the quality of life (QoL) of SBS-intestinal failure patients. However, spontaneous intestinal adaptation along with disease-modifying therapies allow reducing parenteral support, thereby improving QoL., RECENT FINDINGS: During the first years following extensive surgery, spontaneous structural and functional intestinal changes take place which stimulate a more efficient nutrient and fluid absorption in the remaining bowel. Given their potential role in the ileal braking mechanism, enterohormones, such as glucagon-like peptide (GLP)-2, GLP-1, and peptide YY (PYY), promote an accelerated adaptation or hyperadaptation. While the exact role of GLP-1 and PYY in SBS is still being explored, GLP-2 analogs have clearly shown to be effective in improving outcome in SBS., SUMMARY: Whereas spontaneous intestinal adaptation improves the nutritional status of SBS patients to a certain extent, GLP-2 analogs can further decrease parenteral support needs through hyperadaptation. There are, however, other promising candidates on the horizon that - alone or in combination - could possibly establish additional disease-modifying effects.

Parreiras-E-Silva LT, de Araujo IM, Elias J, Jr., Nogueira-Barbosa MH, Suen VMM, Marchini JS, Bonella J, Nahas AK, Salmon CEG, de Paula FJA. Short bowel syndrome: influence of nutritional therapy and incretin GLP1 on bone marrow adipose tissue. Annals of the New York Academy of Sciences. 2018;1415(1):47-56. doi: https://dx.doi.org/10.1111/nyas.13657.

- Energy deprivation leads to a decrease in white adipose tissue and bone mineral density (BMD), while simultaneously inducing the expansion of marrow adipose tissue (MAT). In short bowel syndrome (SBS), parenteral nutrition mitigates the deterioration of nutritional status, including decreases in MAT. Osteoporosis is, however, a frequent complication of SBS. The objective of our study here was to evaluate the association of fat deposit sites (subcutaneous and visceral adipose tissues: intrahepatic lipid (IHL) and MAT) and the incretin glucagon-like peptide 1 (GLP1) with BMD in individuals with SBS. MAT was negatively correlated with lumbar spine BMD in normal individuals, but not in those in the SBS group, who otherwise showed a positive correlation between MAT and GLP1. In addition, in individuals with SBS, IHL was negatively associated with lumbar spine BMD and positively associated with C-terminal telopeptide of type 1 collagen (a serum biomarker of bone turnover). Caloric maintenance in individuals with SBS, therefore, seems to positively affect the relationship between MAT and BMD, which may be modulated, at least in part, by GLP1.

Hvistendahl M, Brandt CF, Tribler S, Naimi RM, Hartmann B, Holst JJ, Rehfeld JF, Hornum M, Andersen JR, Henriksen BM, Brobech Mortensen P, Jeppesen PB. Effect of Liraglutide Treatment on Jejunostomy Output in Patients With Short Bowel Syndrome: An Open-Label Pilot Study. JPEN Journal of parenteral and enteral nutrition. 2018;42(1):112-21. doi: https://dx.doi.org/10.1177/0148607116672265.

- BACKGROUND: An impaired hormonal "ileo-colonic brake" may contribute to rapid gastric emptying, gastric hypersecretion, high ostomy losses, and the need for parenteral support in end-jejunostomy short bowel syndrome (SBS) patients with intestinal failure (IF). Liraglutide, a glucagon-like peptide 1 receptor agonist, may reduce gastric hypersecretion and dampen gastric emptying, thereby improving conditions for intestinal absorption., MATERIALS AND METHODS: In an 8-week, open-label pilot study, liraglutide was given subcutaneously once daily to 8 end-jejunostomy patients, aged 63.4 +/- 10.9 years (mean +/- SD) and with small bowel lengths of 110 +/- 66 cm. The 72-hour metabolic balance studies were performed before and at the end of treatment. Food intake was unrestricted. Oral fluid intake and parenteral support volume were kept constant. The primary end point was change in the ostomy wet weight output., RESULTS: Liraglutide reduced ostomy wet weight output by 474 +/- 563 g/d from 3249 +/- 1352 to 2775 +/- 1187 g/d (P = .049, Student t test). Intestinal wet weight absorption tended to increase by 464 +/- 557 g/d (P = .05), as did urine production by 765 +/- 759 g/d (P = .02). Intestinal energy absorption improved by 902 +/- 882 kJ/d (P = .02)., CONCLUSION: Liraglutide reduced ostomy wet weight output in end-jejunostomy patients with SBS-IF and increased their intestinal wet weight and energy absorption. If larger, randomized, placebo-controlled studies confirm these effects, it adds to the hypothesis that many ileo-colonic brake hormones in conjunction may be involved in the process of intestinal adaptation. By identification of key hormones and addressing their potential synergistic effects, better treatments may be provided to patients with SBS-IF. This trial was registered at clinicaltrialsregister.eu as 2013-005499-16.

Madsen KB, Askov-Hansen C, Naimi RM, Brandt CF, Hartmann B, Holst JJ, Mortensen PB, Jeppesen PB. Acute effects of continuous infusions of glucagon-like peptide (GLP)-1, GLP-2 and the combination (GLP-1+GLP-2) on intestinal absorption in short bowel syndrome (SBS) patients. A placebo-controlled study. Regulatory peptides. 2013;184:30-9. doi: https://dx.doi.org/10.1016/j.regpep.2013.03.025.

- BACKGROUND AND AIMS: The ileocolonic brake is impaired in short bowel syndrome (SBS) patients with distal bowel resections. An attenuated meal-stimulated hormone secretion may cause gastric hypersecretion, rapid gastric and intestinal transit and a poor adaptation. Attempting to restore this ileocolonic brake, this study evaluated the acute effects of continuous intravenous administration of glucagon-like peptide (GLP) 1 and 2, alone or in combination, on gastrointestinal function in SBS patients., METHODS: SBS patients were admitted 4 times for identical 72-h balance studies, where infusions (1 pmol/kg/min) of GLP-1, placebo (saline), GLP-2 and GLP-1+2 (1 pmol/kg/min of each), were provided. Patients filled out a VAS questionnaire regarding subjective symptoms during treatments. Bone mineral content, body-weight and -composition were measured using DEXA scans. Blood glucose, insulin, pro insulin C-peptide and GLP concentrations were measured in relation to a standardized breakfast., RESULTS: Nine SBS patients (5 women/4 men, aged 52+/-11) were enrolled and completed the study; 7 had end-jejunostomies, 2 had 50% of colon-in-continuity. All treatments significantly reduced the fecal wet weight, energy, nitrogen, sodium and potassium losses compared to placebo. However, only GLP-2 containing treatments increased absolute absorption of wet weight and sodium. Only GLP-1+2 improved the hydrational status evaluated by DEXA increases in the fat mass and calculated total body weight. GLP-1 and GLP-1+2 reduced the post-prandial blood glucose levels. A tendency of nausea and reduced appetite was seen in relation to GLP-1 treatment, but this was ameliorated by the co-administration of GLP-2., CONCLUSION: GLP-1 decreased diarrhea and fecal excretions in SBS patients, but it seems less potent than GLP-2. The combination of GLP-1+2 numerically provided additive effects on intestinal absorption compared to either peptide given alone. Larger, long-term studies should further assess the potential of the glucagon-like peptides or analogs, alone or in combination, in the treatment of SBS patients.

Kunkel D, Basseri B, Low K, Lezcano S, Soffer EE, Conklin JL, Mathur R, Pimentel M. Efficacy of the glucagon-like peptide-1 agonist exenatide in the treatment of short bowel syndrome. Neurogastroenterology and motility. 2011;23(8):739-e328. doi: https://dx.doi.org/10.1111/j.1365-2982.2011.01723.x.

- BACKGROUND: Short bowel syndrome (SBS) is a serious clinical disorder characterized by diarrhea and nutritional deprivation. Glucagon-like peptide-1 (GLP-1) is a key hormone, produced by L-cells in the ileum, that regulates proximal gut transit. When extensive ileal resection occurs, as in SBS, GLP-1 levels may be deficient. In this study, we test whether the use of GLP-1 agonist exenatide can improve the nutritional state and intestinal symptoms of patients with SBS., METHODS: Five consecutive patients with SBS based on <=90 cm of small bowel and clinical evidence of nutritional deprivation were selected. Baseline SBS symptoms, demographic and laboratory data were obtained. Antroduodenal manometry was performed on each subject. Each patient was then started on exenatide and over the following month, the baseline parameters were repeated., KEY RESULTS: The subjects consisted of four males and one female, aged 46-69 years. At baseline, all had severe diarrhea that ranged from 6 to 15 bowel movements per day, often occurring within minutes of eating. After exenatide, all five patients had immediate improvement in bowel frequency and form; bowel movements were no longer meal-related. Total parenteral nutrition was stopped successfully in three patients. Antroduodenal manometry revealed continuous low amplitude gastric contractions during fasting which completely normalized with exenatide., CONCLUSIONS & INFERENCES: Exenatide is a novel and safe treatment option for SBS. It produced substantial improvement in the bowel habits, nutritional status and quality of life of SBS patients. Successful treatment with exenatide may significantly reduce the need for parenteral nutrition and small bowel transplant. Copyright © 2011 Blackwell Publishing Ltd.

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A case of hypomagnesemia linked to refractory hypokalemia and hypocalcemia with short bowel syndrome

- Case Reports
- Nihon Jinzo Gakkai Shi. 2012;54(8):1197-202.
- [[Article in Japanese]
- Yuki Sato 1, Yuriko Yonekura, Tatsuo Tsukamoto, Hiroko Kakita, Yuh Tateishi, Toshiyuki Komiya, Satomi Yonemoto, Eri Muso
- Abstract
- We report a case of a 59-year old Japanese woman with short bowel syndrome, whose hypokalemia and hypocalcemia were successfully treated with magnesium (Mg) supplementation. Two years previously, she underwent Mile's operation for advanced rectal cancer, which could have been the cause of subsequent extensive resection of the small intestine by strangulation. After serial resection, she gradually developed chronic diarrhea and anorexia. Three weeks before admission, she developed general fatigue and tetany, and was hospitalized at another hospital. On admission, her serum K and Ca were 2.5 mEq/L and 4.3 mg/dL, respectively, hence regular fluid therapy containing potassium (K) and calcium (Ca) was provided following admission. However, her hypokalemia and hypocalcemia persisted, and she also displayed renal dysfunction and thereafter was transferred to our department for further evaluation and treatment. Since the laboratory tests revealed severe hypomagnesemia (0.4 mg/dL), we started intravenous Mg supplementation together with fluid therapy containing K and Ca. After the combination therapy, her clinical symptoms and electrolyte disorders were remarkably improved within a week. As Mg is essential for PTH secretion in response to hypocalcemia and to inhibit the K channel activity that controls urinary K excretion, hypomagnesemia can cause hypocalcemia and hypokalemia, which is refractory to repletion therapy unless Mg is administered. Therefore, for patients who present with signs of Mg deficiency, early and accurate diagnosis of Mg deficiency should be made and corrected.

SGLT2i and Magnesium

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Journal of Diabetes Investigation

Clinical factors associated with the occurrence of nausea and vomiting in type 2 diabetes patients treated with glucagon-like peptide-1 receptor agonists

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- Conclusions: The present study showed a significant correlation of PPIs or H2RAs, female sex, and diabetic retinopathy with nausea and vomiting in patients with type 2 diabetes treated with GLP-1 RAs. Hence, the occurrence of nausea and vomiting in patients with these factors warrants attention.

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Cannabinoid Hyperemesis Syndrome

J. Eric Fleming, MD and Sean Lockwood, MD

- With the increased prevalence of marijuana use in the U.S. over the past decade and reform in legislation taking place over the next couple of years, it is increasingly important to be able to recognize CHS to avoid frequent hospital utilization and repeated costly evaluations. Cannabinoid hyperemesis syndrome is recognized by the triad of chronic cannabis use, cyclical hyperemesis, and compulsive hot bathing.4
- The syndrome has 3 phases. In the prodromal phase the patient has morning predominance of nausea, usually without emesis. This is followed by the hyperemesis phase, which is characterized by hyperemesis, vague abdominal pain, and learned compulsive hot bathing.
- The third phase is the recovery phase, which is a return to normal behavior. During the recovery phase, if patients cease marijuana use, they remain asymptomatic; however, if patients continue to use marijuana, they often have recurrence of the hyperemesis phase.5 The diagnosis of cannabinoid hyperemesis syndrome is difficult as it is a diagnosis of exclusion. Patients may present to the ED many times prior to diagnosis.

Cannabinoid Hyperemesis Syndrome

- The major CHS features that suggest the diagnosis are
  - severe cyclic nausea and vomiting,
  - relief of symptoms with abstinence from cannabis,
  - temporary symptom relief with hot bathing,
  - abdominal pain,
  - at least weekly use of marijuana.
  - Other supportive features include aged < 50 years, weight loss > 5 kg, symptoms that are worse in the morning, normal bowel habits, and negative evaluation, including laboratory, radiography, and endoscopy
- CHS often presents with refractory, self-limited nausea and vomiting with vague abdominal pain that is temporarily relieved by hot baths or showers.
- In the largest case series, the majority of subjects used marijuana **at least weekly for > 2 years**.
- Many studies categorize CHS into 3 phases: prodromal, hyperemetic, and recovery.

- The prodromal, or preemetic phase, is characterized by early morning nausea without emesis and abdominal discomfort.

CHS

- The only cure for CHS is to stop using cannabis. Hot baths may relieve the nausea for a while, but they don’t cure CHS. Taking too many hot baths can increase dehydration due to sweating.

- You may use home treatments to relieve CHS symptoms immediately after quitting cannabis. These remedies may help you feel better while you transition to the recovery phase. Your healthcare provider may recommend:

- Antihistamines, like diphenhydramine (Benadryl®).
- Capsaicin cream to relieve pain.
- Pain relievers like ibuprofen (Advil®, Motrin®) or acetaminophen (Tylenol®).
- Prescription medications, including benzodiazepines (like lorazepam), antipsychotic medications (like haloperidol) or tricyclic antidepressants.