

THE ROLE OF NATUROPATHIC ONCOLOGY IN
CARCINOID SYNDROME AND NEUROENDROGINE
NEOPLASIA

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CONTACT INFORMATION

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WHAT IS NATUROPATHIC MEDICINE

- Naturopathic Doctors as a group are a provincially regulated health care profession.
- Some Naturopathic Doctors may seek extra training and credentials in Naturopathic Oncology.
 - Fellow of the American Board of Naturopathic Oncology
 - Completion of a residency (Canadian and US)
 - Proof of patient case load
 - Publications and research
 - Successful completion of a board certification examination

NATUROPATHIC MEDICINE

- A naturopath with sufficient training in oncology can:
 - Support the patient through conventional treatment
 - Help to manage side effects
 - Modalities used: Herbs, vitamins, minerals, intravenous therapy and other injections, acupuncture, lifestyle counselling
 - *Properly* ensure no interactions between medications and nutraceuticals/herbs/natural health products

- For cross referencing NHPs and drugs, we use TRC Natural Medicines Database as a starting point.
- Thorough search for any publications which have used the combination
- Another search for common interactions: CYP450 complex and PGP

NATUROPATHIC MEDICINE

- A naturopathic doctor should never be claim to provide an alternative treatment plan to replace conventional medicine.
- Naturopathic doctors are merely supportive in nature
- Use an *evidence based approach* utilizing the best available evidence that we have

ARE NATURAL HEALTH PRODUCTS BEING USED BY NET PATIENTS?

[Scand J Gastroenterol](#). 2019 Aug 1:1-5. doi: 10.1080/00365521.2019.1646799. [Epub ahead of print]

Use of biologically based complementary medicines in patients with neuroendocrine tumors.

[Borre M](#)¹, [Dam GA](#)¹, [Grønbaek H](#)¹.

[Author information](#)

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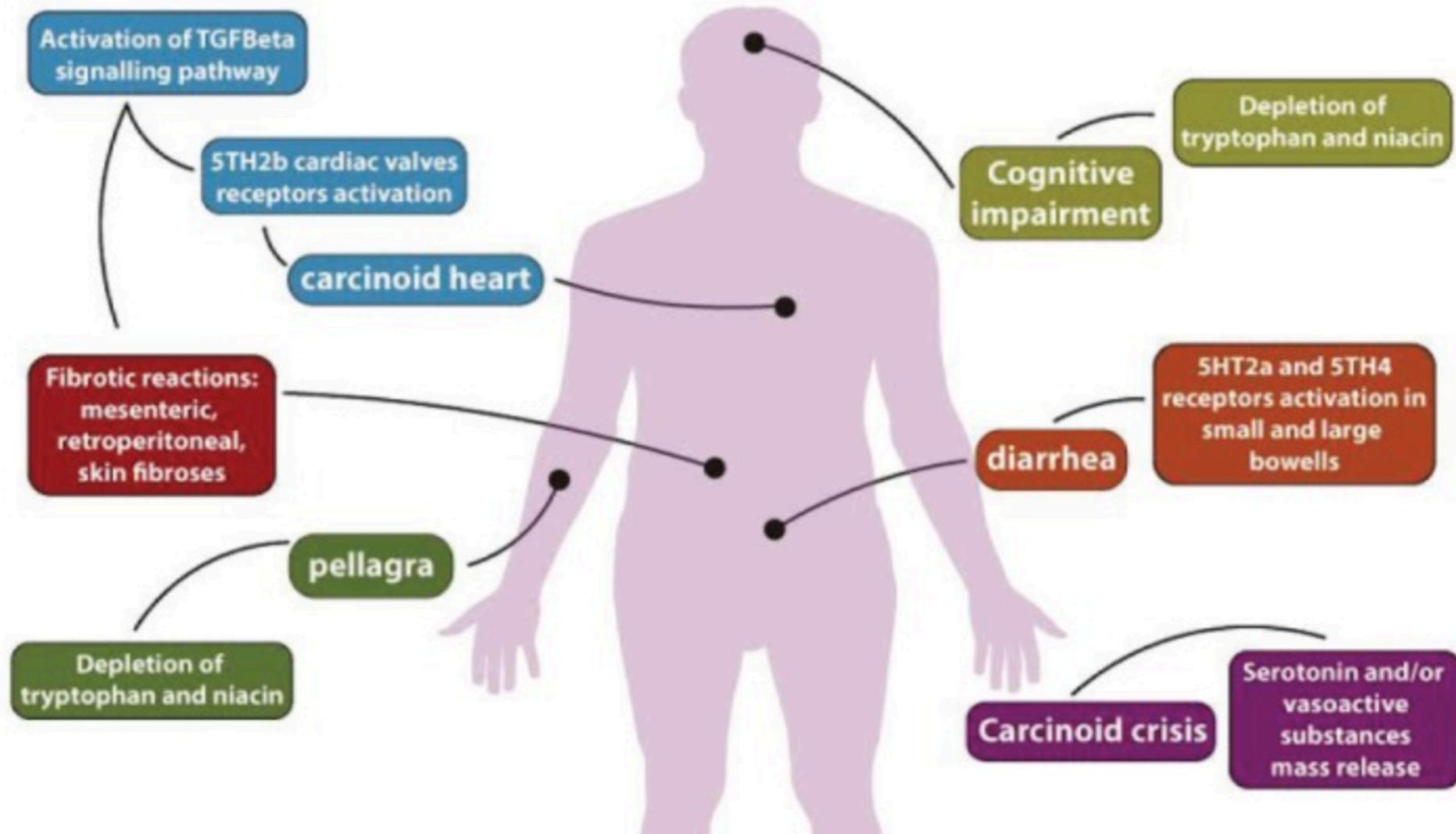
a Department of Hepatology and Gastroenterology, Aarhus University Hospital ENETS Centre of Excellence, Aarhus University Hospital , Aarhus , Denmark.

Abstract

Background: Biologically based complementary medicines (BB-CMs) are popular in patients with cancer. However, there are only limited data for BB-CMs in patients with neuroendocrine tumors (NET). We aimed to identify the prevalence and type of BB-CM use and the association to the nutritional risk score (NRS-2002) in NET patients. **Methods:** We performed a cross-sectional questionnaire study in NET outpatients at the Department of Hepatology and Gastroenterology at Aarhus University Hospital. The nutritional risk was determined by the NRS-2002. **Results:** We included 186 patients (51% women, median age 66 years). Sixty-six percent were regular BB-CM users. Forty-two percent used at least two supplements. The most popular BB-CMs were **vitamin and mineral supplements (47%), calcium and vitamin D (34%)**. One-third used non-vitamin non-mineral supplements such as **fish oil, herbs, Ginger, Q-10, garlic and probiotics**. The use of BB-CMs was associated with female gender (48% vs. 37%, $p < .05$). Intake was significantly more frequent among patients with an NRS score ≥ 3 , (60% vs. 76%) and in patients with change in performance status (58% vs. 76%), ($p < .05$, all). Patients reporting dietary changes used BB-CMs more frequently than patients without dietary changes (61% vs. 77%) ($p < .05$). **Conclusions:** In our study, 66% percent of NET patients use BB-CM and 42% used two or more supplements. Vitamins with and without herbal ingredients, minerals, calcium, vitamin D, and fish oil were the most popular supplements. The use of BB-CMs was associated with an NRS score ≥ 3 , change in dietary intake, female gender, and change in ECOG performance status.

SEQUELAE FROM NETS

ECANCERMEDICALSCIENCE. 2016 AUG 8;10:662



MALNUTRITION

[World J Gastroenterol](#). 2019 Mar 14; 25(10): 1171–1184.

Published online 2019 Mar 14. doi: [10.3748/wjg.v25.i10.1171](https://doi.org/10.3748/wjg.v25.i10.1171)

PMCID: PMC6421241

PMID: [30886501](https://pubmed.ncbi.nlm.nih.gov/30886501/)

Nutritional and vitamin status in patients with neuroendocrine neoplasms

[Dominique SVM Clement](#), [Margot ET Tesselaar](#), [Monique E van Leerdam](#), [Rajaventhana Srirajaskanthan](#), and [John K Ramage](#)

- *Malnutrition is present in up to 40% of patients with neuroendocrine neoplasms.*
- Patients with gastroenteropancreatic located neuroendocrine neoplasms have a high risk of malnutrition and vitamin deficiency. Multidisciplinary treatment focussing on diarrhea and nutritional status is warranted.

DE HOSSON ET AL

NUTRIENT DEFICIENCIES (DIVIT)

Towards Optimal Personalized Diet and Vitamin Supplementation in Patients With a Neuroendocrine Tumor

DIVIT Study Diet and Vitamin Supplementation in Patients With a Neuroendocrine Tumor

- March 2018 paper recognizing common nutrient deficiencies and feasibility of personalized dietary advice and supplementation of deficient vitamins (DIVIT) in NET patients.

NUTRIENT DEFICIENCIES

- Symptoms of gastroenteropancreatic neuroendocrine tumours often include *abdominal pain and/or diarrhea* which can influence patients nutritional status.
- Most common nutrient deficiencies:
 - *Fat-soluble vitamins*
 - *Vitamin A, Vitamin D, Vitamin E, Vitamin K*
- Little knowledge exists on trace elements status, but this can be tested using laboratory testing (nutrient panels exist, but not often through conventional MDs). Most common deficiencies include: cobalt, copper, fluorine, iodine, selenium and zinc.

NUTRIENT DEFICIENCIES

- Several factors in neuroendocrine tumour patients may lead to malnutrition:
 - Protein, carbohydrate and lipid metabolism are altered resulting in increased metabolic resting rate, insulin resistance, lipolysis (break down of fat) and proteolysis (break down of protein).
 - This can lead to weight loss
 - If this process continues, cancer cachexia can develop (muscle wasting)

COMMON NUTRIENT DEFICIENCIES

Supplementation of Vitamin D Deficiency in Patients with Neuroendocrine Tumors Using Over-the-Counter Vitamin D3 Preparations.

[Robbins HL](#)¹, [Symington M](#)¹, [Mosterman B](#)¹, [Goodby J](#)¹, [Davies L](#)¹, [Dimitriadis GK](#)², [Kaltsas G](#)¹, [Randeve HS](#)^{1,2,3}, [Weickert MO](#)^{1,2,3}.

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Abstract

Vitamin D (vit-D) deficiency is highly prevalent in patients with gastro-entero-pancreatic neuroendocrine tumors (GEP-NET) and has been linked to reduced overall survival. We here assessed the vit-D status in 183 patients with GEP-NET at the time of their first presentation in the ARDEN NET Centre. We further examined the effect of simple advice to increase vit-D intake using over-the-counter vit-D preparations [colecalciferol (Vit-D3), 1,000-2,000 units/day], over a prospective observation period of 24 mo. At baseline, only 33.3% of patients showed vit-D sufficiency (25-OH-vit-D; >50 nmol/L), the remainder was insufficient (31.3%; 25-OH-vit-D; 25-50 nmol/L) or deficient (35.5%; 25-OH-vit-D; <25 nmol/L). Repeated advice to increase vit-D intake at routine 6-monthly follow-up appointments was associated with increased 25-OH-vit-D from 37.8 ± 3.5 nmol/L at baseline to 60.4 ± 5.6 nmol/L ($P < 0.0001$) and 56.8 ± 7.0 nmol/L ($P = 0.039$) after 12 and 24 mo. Percentage of vit-D insufficiency decreased from 66.6% at baseline to 44.9% and 46.2% after 12 and 24 months, respectively. Previous abdominal surgery, but not treatment with somatostatin analogues predicted 25-OH-vit-D levels in bootstrapped linear regression analyses ($P = 0.037$). **In summary, simple advice to increase vit-D intake using over-the-counter preparations was associated with significant improvement of vit-D deficiency/insufficiency, although, 15% of GEP-NET patients remained deficient and may benefit from additional measures of vit-D replacement.**

Vitamin D and vitamin B12 deficiencies are common in patients with midgut carcinoid (SI-NET).

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Author information

1 Clinical Nutrition Unit, Department of Gastroenterology and Hepatology, Sahlgrenska University Hospital, Gothenburg, Sweden.

2 Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden.

Abstract

BACKGROUND/OBJECTIVES: Patients with small intestinal neuroendocrine tumours (SI-NET) often have diarrhoea from hormonal overproduction, surgery and medical treatment, leading to malabsorption of bile salts, fats, vitamin B12 and fat-soluble vitamins. This could lead to malnutrition.

SUBJECTS/METHODS: We assessed nutritional status in 50 consecutive out patients with disseminated SI-NET, 25 patients in each cohort. The first cohort was descriptive and the second cohort supplemented with vitamin D, B12 and calcium. Vitamin D deficiency was defined as <50 nmol/l. All patients were assessed by clinical chemistry and dual-energy X-ray absorptiometry (DXA) and interviewed about weight changes, appetite, gastrointestinal disorders, sunhabits and the use of supplements.

RESULTS: In the first cohort, 29% of the patients were severely and 17% moderately vitamin D deficient. In patients without prior substitution, 32% had subnormal vitamin B12 levels. Seventy-six percent had low bone density. In the second cohort with vitamin and mineral supplementation, none had severe vitamin D deficiency, but 28% had moderate deficiency. No patient had subnormal vitamin B12 levels. Sixty percent had low bone density. The serum levels of vitamin D and B12 were higher and parathyroid hormone (PTH) lower in the second cohort compared with the first cohort ($P \leq 0.022$). Vitamin D and PTH were negatively correlated, $r = -0.30$, $P = 0.036$.

CONCLUSIONS: Low serum levels of vitamin D and vitamin B12, and low bone density are common in patients with disseminated SI-NET. Supplementation of vitamin D, B12 and calcium resulted in higher serum levels of vitamins, lower PTH levels and diminished severe vitamin D deficiency and is thus recommended as standard care.

HOW TO TEST AND SUPPLEMENT WITH VITAMIN D

- *25 hydroxy D3* is the blood (serum) test to determine vitamin D status.
 - *Testing frequency: Every 3 months
- Reference range in Canada is 75-250 umol/L
- Typical "blanket dose:" 2000 IU/day. This may not be enough to treat or prevent a deficiency especially if there is malabsorption in the small intestine.
- In extreme cases of malabsorption, injections may be required (intramuscularly).

CONSEQUENCES OF LOW VITAMIN D

- Low bone mineral density:
 - In 2016 cohort study in previous slide, 60% had low bone mineral density
 - Increased risk of fracture

CONSEQUENCES OF LOW VITAMIN D

- Low levels of vitamin D may negatively affect overall survival and progression free survival.

CONSEQUENCES OF LOW VITAMIN D

[Neuroendocrinology](#). 2017;105(4):403-411. doi: 10.1159/000456619. Epub 2017 Jan 26.

Impact of Vitamin D on the Clinical Outcome of Gastro-Entero-Pancreatic Neuroendocrine Neoplasms: Report on a Series from a Single Institute.

[Massironi S](#), [Zilli A](#), [Bernasconi S](#), [Fanetti J](#), [Cavalcoli F](#), [Ciafardini C](#), [Felicetta J](#), [Conte D](#).

[Author information](#)

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Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Abstract

BACKGROUND/AIMS:

Vitamin D deficiency is hypothesized to represent a risk factor in several neoplasms. The aim of this study was to determine whether serum 25-hydroxyvitamin D (25-OHvitD) deficiency represents a risk factor for neuroendocrine neoplasms (NENs) and can be associated with overall survival (OS) and progression-free survival (PFS).

METHODS:

From 2010 to 2015, 138 patients with gastro- entero-pancreatic NENs (61 females; median age, 63 years) were included in the study. Serum 25-OHvitD levels, which were measured at baseline, were defined as deficient if ≤ 20 ng/mL. In such cases, 25-OHvitD supplementation was administered to the patients. The possible associations between 25-OHvitD levels and disease grading, staging, overall OS, and PFS were considered. Furthermore, the possible association between 25-OHvitD supplementation and PFS or OS was evaluated by Cox proportional hazards regression.

RESULTS:

Median 25-OHvitD levels were 12.9 ng/mL (range 2-32); in detail, 94 patients (68%) had ≤ 20 ng/mL, with 46 cases (33%) having ≤ 10 ng/mL. An inverse correlation was observed between 25-OHvitD levels and OS ($p = 0.03$, $r_s = -0.18$) and PFS ($p = 0.01$, $r_s = -0.22$). At Cox proportional hazards regression, mortality was not related to 25-OHvitD levels; however, there was an association between 25-OHvitD supplementation and OS ($p < 0.002$).

CONCLUSIONS:

Vitamin D deficiency is highly prevalent among NEN patients. 25-OHvitD supplementation potentially plays an important role in the correction of 25-OHvitD values, and has an influence on the clinical outcome. However, further studies are needed to confirm this observation.

OTHER NUTRIENT DEFICIENCIES

VITAMIN K

- "Two studies report on the status of fat-soluble vitamins in patients with NEN. Fiebrich et al[34] analysed the fat soluble vitamin status of 35 patients with metastatic small intestinal NEN on treatment with somatostatin analogues for at least 18 mo. Eighty percent of patients showed abnormally low levels of at least 1 fat soluble vitamin and 32% of patients showed multiple deficiencies."
- 69% of patients were deficient in vitamin K1. In 12% of patients vitamin K1 deficiency resulted in prolonged prothrombin time (bleeding time was increased).

OTHER NUTRIENT DEFICIENCIES

VITAMIN B3 (NIACIN)

- Vitamin B3 (too much Tryptophan is shunted to Serotonin in CS and NET and can result in a B3 (niacin) deficiency known as Pellagra).
- Tryptophan is both a precursor to SEROTONIN and B3
- Niacin may be supplemented if a patient has symptoms of *Pellagra* ("3 D's": Diarrhea, dementia and dermatitis. May also be associated with depressive symptoms).
- Niacin may cause flushing when supplemented. Some patients do not experience this symptom if they take it with baby aspirin. There are also no flush versions available. Start with a low dose. Typical doses available are 100 mg and 500 mg/capsule.

NIACIN

- How to prevent niacin deficiency through *diet*:
 - Eat protein rich foods such as: meat, poultry, fish, eggs, nut butters, beans, lentils, soy

- New guidelines should include appropriate screening for malnutrition as part of routine care.
- Nutrient levels can be checked through a blood test, but comprehensive panels are not often run.

- Nutritional status can also be measured based on the following (commonly done):
 - Body Mass Index (BMI)
 - Biochemical markers: serum proteins such as albumin or transferrin
 - Body composition (BIA assesses fat free versus fat mass)

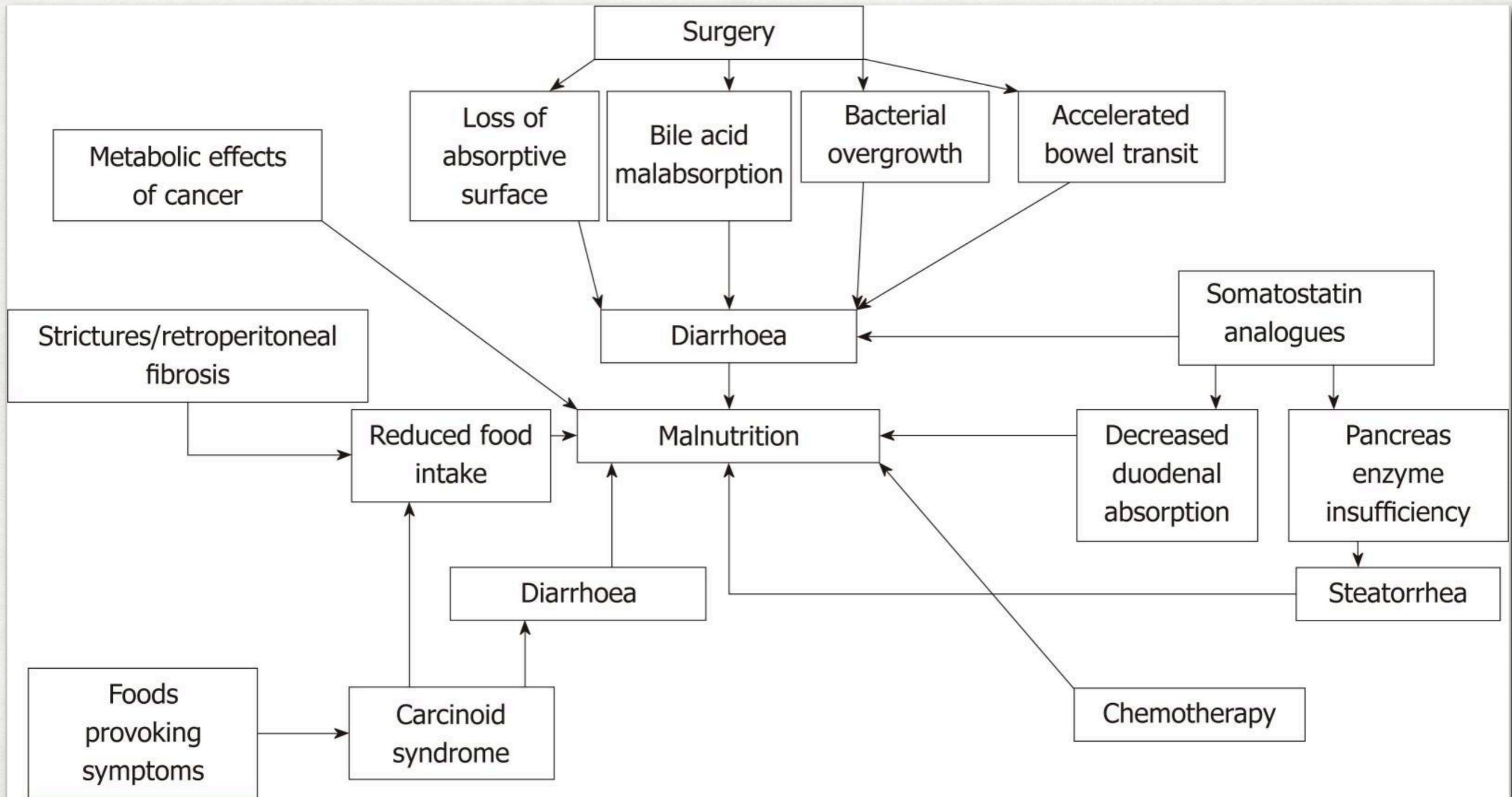
MALNUTRITION

- **Factors influencing the development of malnutrition:**
 - **SIZE** and **LOCATION** of the primary tumour
 - **SIDE EFFECTS** from treatment
 - **Hormone production** of the tumour itself

- Leading cause of malnutrition is *diarrhea* which leads to dehydration and electrolyte disturbances.
- Treatment of diarrhea should be guided by its cause:
 - Multidisciplinary treatment including dietician support is necessary for all malnourished patients with NETs.

CAUSES OF MALNUTRITION

CLEMENT, 2019



CAUSES OF MALNUTRITION

- **SURGICAL CAUSES:**

- Whipple Procedure (resulting enzyme deficiencies)
- Short bowel syndrome (leads to fluid imbalance and reduced transit time, loss of absorptive surface)
- Terminal ileum: B12 deficiency, bile acid malabsorption



**DIARRHEA,
MALABSORPTION,
BACTERIAL OVERGROWTH
(SIBO)**

SOMATOSTATIN ANALOGUE ASSOCIATED MALNUTRITION

SOMATOSTATIN

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graph TD; A[SOMATOSTATIN] --> B[DECREASED ABSORPTION OF CARBOHYDRATES AND FAT]; B --> C[DECREASED PANCREATIC ENZYME SECRETION]; C --> D[STEATORRHEA AND MALABSORPTION];
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DECREASED ABSORPTION OF CARBOHYDRATES AND FAT

DECREASED PANCREATIC ENZYME SECRETION

STEATORRHEA AND MALABSORPTION

SYMPTOMS TO MANAGE

- Diarrhea and malabsorption:
- Drugs that may be helpful, in addition to SSA (Somatostatin analogue) therapy (octreotide/lanreotide) to reduce hormone levels:
 - Cholestyramine (bile acid sequestrant), Telotristat (Xermelo)
 - Butyric acid
 - Diosmectite clay
 - Slippery elm, marshmallow root (powder form works best)
 - Probiotics (may have to use some trial and error here to determine which one might help the most).

DIARRHEA CONTROL

- In my clinical experience, I have seen the following be helpful:
- Probiotics:
 - *Saccharomyces boulardii*
 - Cytomatrix Multistrain 11 (combination of Bifidobacterim, lactobacillus and *S. Thermophilus*)
 - Fermented foods (Kombucha (fermented tea beverage), Kefir (coconut), Kimchi, Sauerkraut and other fermented vegetables)
- **Prebiotics:** Soluble fibres

DIARRHEA CONTROL CONTINUED

- Brush border enzyme deficiencies? Cannot really test for this.
 - Lactose, maltose may aggravate diarrhea if not broken down properly.
 - Sugar alcohols can also be aggravating: Xylitol, malitol, sorbitol, etc.
 - *Digestive enzymes* may be helpful in some cases, to help break down aggravating disaccharides (linked sugars).
- In patients who have had a Whipple Procedure, it is often helpful to prescribe a comprehensive digestive enzyme in conjunction with the prescribed enzymes.

ENZYME COMBINING

- If Creon or equivalent is not effective on its own, or the patient is not finding the correct dose easily for the amount of food consumed:
 - Trial and error with various enzyme products (usually containing a combination of enzymes that break down: protein, carbohydrates and fat).

DEHYDRATION

IS THERE ANYTHING BETTER THAN GATORADE?

- Nuun tablets (stevia sweetened electrolyte tablet), Roar (does contain erythritol and cane sugar).
- G2 and alternative, artificial sweeteners can be irritating to the GI tract and may worsen diarrhea and stomach upset
- Coconut water should be diluted as it may have a laxative effect if used full strength (1/2 water, 1/2 coconut water)

TRANSIT TIME

FOODS

- Finding the right balance of fat, starch and salt is often helpful.
- Salted Mashed potatoes and/or baked potato, cassava root chips have been very helpful for some patients.

EXACERBATING FOODS

- AMINES (Tyramine is the most active amine and may trigger the production of catecholamines): Foods high in amines may be more aggravating for some patients than others.

FOODS **LOW** IN AMINES

- Meat, poultry, fish
- Most vegetables—but cooked may be better tolerated than raw
- Fruits in moderate amounts with the exception of banana, avocado, raspberries
- Grain foods, starchy foods—lower fiber or soft cooked grains may be most tolerated
- Un-aged cheeses
- Soy

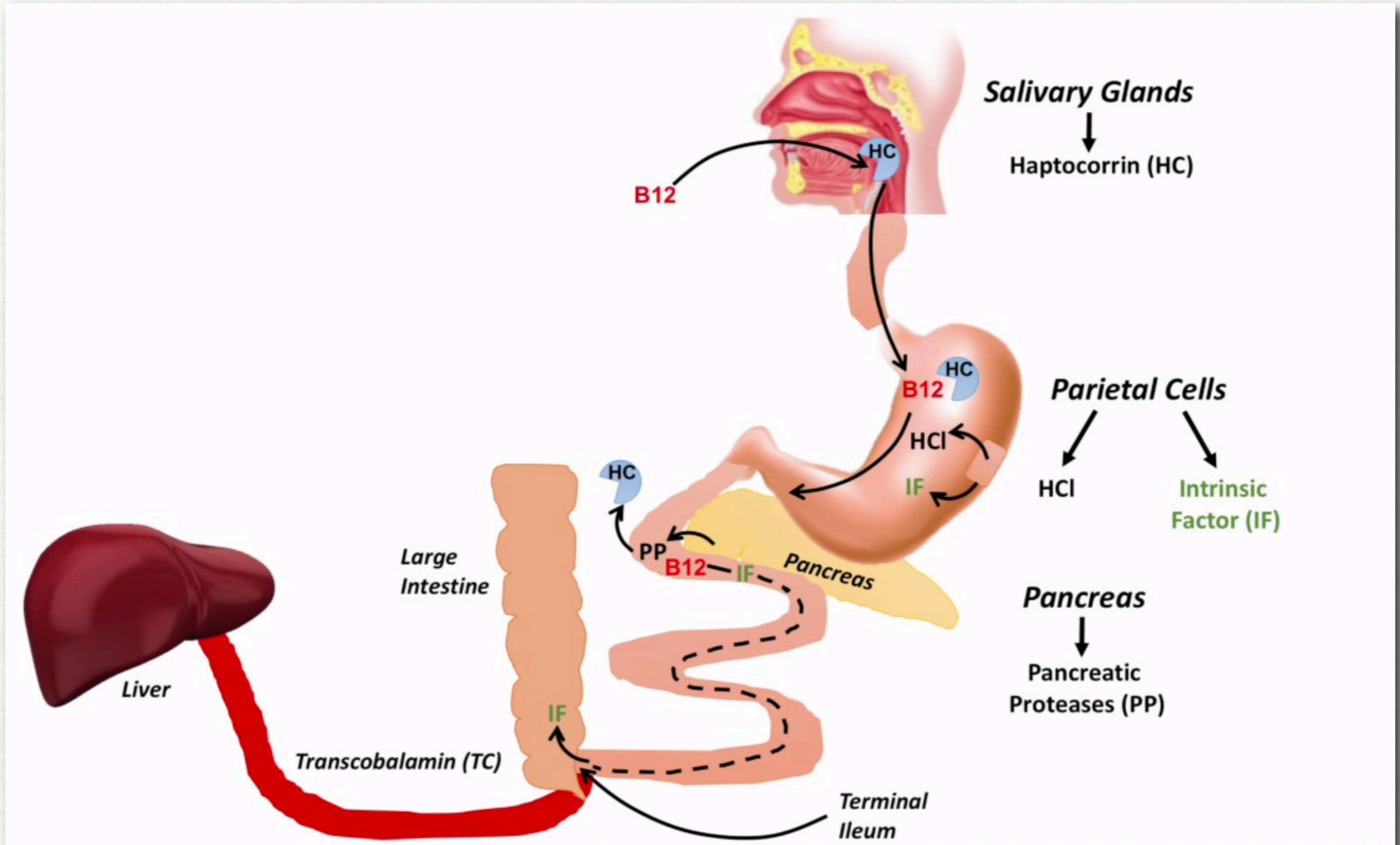
FOODS HIGH IN AMINES

- Aged cheeses
- Alcohol
- Smoked or processed meats.
- Yeast extracts (including Brewer's Yeast)
- Broad beans
- Caffeine containing drinks, coffee (in large amounts), soda
- Chocolate (in large amounts)

ENERGY LEVEL

- Fatigue is common in NET patients
- What can help and/or what may be part of the cause?
 - **B12 level** is important to correct if it is deficient (as mentioned in study in Slide #14, it is a common deficiency): Supplement accordingly, and consider B12 injections (intramuscular) if sublingual lozenges are ineffective.
 - Consider checking and re-checking B12 to ensure correction in level.

B12 ABSORPTION



CONSEQUENCES OF LOW B12

- Cardiac concerns (homocysteine)
- Suboptimal cognitive function
- Suboptimal energy level
- Methylation

ENERGY/CARDIAC

- Coenzyme Q10
 - "Intracellular antioxidant"
 - Increased uptake by brain and heart mitochondria
 - Ubiquinone/Ubiquinol: 100-200 mg/day

CARDIAC CONCERNS

- Tricuspid or pulmonary valve are most commonly affected.
- Left side of the heart is less commonly affected unless metastatic disease.
- Conventional management includes on occasion anticoagulation, and management based on symptoms (i.e. diuretics for edema, etc).
- What can we give for cardiac support?
 - Ensure B12 levels are adequate (homocysteine is indirectly associated with B12 level and directly associated with heart disease)
 - CoQ10
 - Omega 3 fatty acids
 - Anti-hypertensive herbs or magnesium bisglycinate as needed

ADAPTOGEN HERBS

ENERGY LEVEL

- Adaptogen herbs (herbs that support adrenal function and therefore energy level):
 - Withania (Ashwagandha)
 - Holy basil
 - Teas
 - Tinctures
 - Standardized extracts in capsules/tablets

COGNITIVE FUNCTION

ANN SURG. 2014 FEB;259(2):355-9

- Patients with carcinoid syndrome report the following with respect to cognitive testing:
 - Weakness in initiation of thoughts
 - Processing speed
 - Visual memory deficits, cognitive efficiency, and delayed verbal recall

COGNITIVE FUNCTION

- Serotonin is produced from its tryptophan which is also a precursor of Niacin.
- In carcinoid syndrome, excessive production of serotonin causes depletion of tryptophan and decreased production of niacin as a result.
- This leads to niacin deficiency symptoms, namely pellagra, which can also contribute to the psychiatric symptoms (low mood).
- In the brain, serotonin is dependent on the availability of tryptophan. Only L- tryptophan or free tryptophan [unbound to albumin] can enter the brain by crossing the blood brain barrier.

COGNITIVE FUNCTION/SUPPORT

- In serotonin/tryptophan/niacin mediated cognitive decline: Improving nutrient status as much as possible should be helpful in supporting these patients.
- Omega 3 fatty acids in general have been helpful in a number of studies in patients with neurocognitive decline.
- Supplementation with niacin and/or methylcobalamine (a specific form of B12) may also be helpful- correct the deficiency based on the blood level.

OTHER THERAPIES

- Acupuncture- symptom specific
- Infusion therapy- What can be administered and why?

- Questions?

- Should you come off of supplements if you have been on them long-term?
- Will long-term supplementation impact the liver and kidneys?
 - EGCG (green tea extract) in high doses
 - Coriolus, other mushrooms? Quality? Contamination and pre-existing conditions?

- Can cancer patients truly boost their immune system to support the body's fight against the cancer?
 - Normally assessed on a case by case basis
 - If necessary, agents would be recommended based on the Differential in a CBC (WBC, neuts, lymphos).
 - Mistletoe, herbal supplements.

- Are there particular foods that are important for cancer patients to consume to aid in fighting cancer?
- What impact do preservatives and processed food have on our body and its ability to fight off diseases and cancer?
- General recommendation is to eat whole and homemade foods where possible. High fat diets are not generally recommended in CS or NETs. The diet should be plant product focused with "low glycemic," fibre rich grains, and "clean" sources of animal protein.
- As mentioned previously- sugar alcohols and additionally preservatives may worsen symptoms.

- Are all supplements made alike? How can we be sure that the content of the supplements is truly what the label says?