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Nutritional Complications and the Management of Patients with Gastroenteropancreatic Neuroendocrine Tumors

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Keywords

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Abstract

Neuroendocrine tumors (NETs) have increased in incidence and prevalence over the past 2 decades and affect approximately 170,000 people in the United States alone. Gastroenteropancreatic (GEP) NETs (GEP NET) are a heterogeneous group of rare tumors that have distinct effects on the body due to their tumor location and potential to secrete hormones and peptides. Clinical practice guidelines and consensus guidelines for GEP NETs with regard to best practice for diagnosis, treatment, and medical management are available, but the supportive care needs and optimal nutritional management of patients affected by these unique tumors remain under-researched: evidence to guide clinical practice is lacking. The pathophysiology of the disease and its treatment can cause various symptoms that can have significant effects on vitamin synthesis and absorption, dietary habits, weight change, and appetite. Deficiency of fat-soluble vitamins and niacin exists amongst patients with GEP NET, particularly those on treatment with somatostatin analogs and with serotonin-secreting tumors, respectively. Malnutrition and dietary modification amongst patients with GEP NET is more prevalent than initially thought: up to 25% of inpatients with GEP NET are malnourished. Food intolerance is also reported in up to 40–90% of these patients, though its misdiagnosis is common. This review summarizes the evidence regarding the impact of GEP NET and its treatment on nutritional factors in these patients with emphasis on malnutrition, vitamin deficiencies, dietary intake, and quality of life. Recommendations for clinical practice and research approaches to address these nutritional issues are discussed.

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors, most commonly located in the gastrointestinal system and lung [1]. Incidence and prevalence of NETs has increased significantly in the past 2 decades [2], and the prevalence of NETs is currently greater than other gastrointestinal cancers (gastric, pancreatic, esophageal, hepatobiliary adenocarcinomas) [2, 3]. Gas-

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trointestinal NETs or gastroenteropancreatic (GEP) NETs account for around 60% of all diagnosed cases and are located in the small intestine, pancreas, and colon; and less commonly in the stomach [3, 4]. GEP NETs are considered a rare and complex disease requiring specialized multidisciplinary consultation and management [3, 5, 6].

Patients with GEP NETs can experience numerous and complex symptoms relating to the local and systemic sites of their disease, paraneoplastic hormonal syndromes or various treatment modalities [7, 8]. Symptoms are often related to the hypersecretion of hormones and peptides (such as serotonin, gastrin, glucagon, and insulin) which can lead to specific hormonal hypersecretory syndromes such as carcinoid syndrome, diabetes mellitus, hypoglycemia, and hypergastrinemia (Zollinger-Ellison syndrome) [3, 9]. These syndromes can hence lead to fatigue, secretory diarrhea, flushing, and abdominal discomfort [8, 10]. The complex pathophysiology, symptoms, and treatment of NETs thus have the potential to significantly impact a patient's nutritional status through their effects on dietary intake, digestion, and nutrient absorption.

Research indicates that patients with GEP NET may be at risk of various nutritional issues including nutrient malabsorption, vitamin deficiencies, food intolerance, and malnutrition. Recent review articles have discussed the nutritional impacts of NETs and suggested that nutrition is an essential component of the assessment and management of these patients [11, 12]. The impact of body composition and metabolic syndrome on NETs and patient outcomes was a particular focus of these reviews though not all literature related to nutrition and NETs was discussed. A comprehensive and detailed evaluation of all available nutrition-related literature is warranted, as is the provision of evidence-based nutrition recommendations for all aspects of nutrition including nutritional status, diet, and vitamin deficiencies. In preparation for this review a literature search was undertaken up to February 2019 to obtain published literature for original clinical studies, observational studies, systematic reviews, and meta-analyses using the following databases: MEDLINE, PubMed, EMBASE, and CINAHL. A keyword-based search was performed using various terms in combination (neuroendocrine tumor OR carcinoid OR neuroendocrine cancer OR neuroendocrine carcinoma) AND (gastrointestinal OR GEP OR pancreatic OR gut OR intestine* OR colorectal OR colon) AND (malnutrition OR nutrition OR diet* OR food OR vitamin OR niacin OR weight OR malabsorption). A total of 676 articles were found and their abstracts assessed for eligibility. Articles were deemed eligible for inclusion if they reported data related to nutrition (malnutrition, diet, food, vitamins or symptoms) and GEP NETs. Only articles published in English were included for analysis. Reference lists from eligible articles were manually searched to identify further relevant articles. A total of 13 original or observational studies, 3 narrative reviews, and 1 published abstract met the eligibility criteria. No systematic reviews or meta-analyses met the eligibility criteria. This review provides a comprehensive overview of current available literature and knowledge regarding the nutritional complications of patients with GEP NETs. The state of evidence guiding an approach to screening and management of nutrition issues is discussed along with current recommendations for practice.

Symptoms and their Nutritional Impacts

Symptoms experienced by patients with NET can result from the tumor mass effect (from primary or metastases), generalized symptoms of malignancy, side-effects of hormonal hypersecretion or related to side-effects of the patient's cancer treatment [3, 6]. Side-effects related to GEP NET, including those with a potential to impact nutrition, are summarized in Table 1. The most prevalent reported symptoms in patients with GEP NET include diarrhea, fatigue, abdominal discomfort, flushing, and food intolerance (Table 2). Up to 30% of patients with GEP NETs, in particular mid-gut NETs (located in the jejunum, ileum, and proximal colon), have carcinoid syndrome, whereby their tumors secrete serotonin and other endogenous amine hormones [6, 13]. Such hypersecretion can give rise to symptoms of flushing (70–80% of cases), fatigue, severe secretory diarrhea (50–80% of cases), food intolerance, restlessness, and fluctuations in mood and pain (40% of cases) [6, 8, 14, 15]. NET-related symptoms can persist for prolonged periods, both predating and after the diagnosis, and these symptoms have a significant impact on the patients' well-being with the potential to markedly reduce QOL [8, 16–21].

There are various treatment modalities used for disease and symptom control in patients with GEP NETs, and include surgery (curative or debulking), somatostatin analog treatment (SSA: lanreotide or octreotide), chemotherapy, peptide-receptor targeted radiotherapy, and targeted therapies such as everolimus and sunitinib [13]. Each of these treatments has the potential to cause side-effects and symptoms that impact QOL and nutritional health (Table 3).

Table 1. Effects of GEP NET on symptom presentation [3, 6, 8]

Presence of malignancy					
Fatigue Low appetite Weight loss General malaise Nausea					
Tumor mass					
primary tumor	metastasis				
Pain Organ dysfunction Low appetite	Pain Organ dysfunction Liver: pain, nausea, fatigue, loss of appetite, fever Peritoneum: pain, bowel obstruction, ascites, bleeding Lung: shortness of breath, cough Lymph nodes: pain, compression of adjacent structure causing dysfunction				
Tumor location					
small intestine	colon/rectum	pancreas	stomach		
Bowel obstruction Bowel ischemia Nutrient malabsorption Steatorrhea Diarrhea Abdominal pain Bleeding	Bowel obstruction Bowel ischemia Diarrhea Abdominal pain Bleeding	Altered blood glucose Altered exocrine enzyme function Nutrient malabsorption Diarrhea Steatorrhea Abdominal pain Biliary obstruction	Early satiety Abdominal pain Reflux/heartburn Bleeding Obstruction		
Hormone secretion (tumor type)					
serotonin (carcinoid)	insulin (insulinoma)	gastrin (gastrinoma)	glucagon (glucagonoma)	vasoactive intestinal peptide (VIPoma)	somatostatin (somatostatinoma)
Flushing Fatigue Diarrhea Food intolerance Pain Small bowel ischemia Carcinoid heart disease Pellagra	Hypoglycemia Dizziness Headache Weakness Confusion Loss of consciousness	Peptic ulceration Abdominal pain Diarrhea Heartburn Weight loss Bleeding	Hyperglycemia Glucose intolerance Diarrhea Weight loss Necrolytic migratory erythema	Severe diarrhea Hypokalemia Dehydration	Diabetes Cholelithiasis Steatorrhea Diarrhea Weight loss

GEP NET, gastroenteropancreatic neuroendocrine tumors.

Diarrhea is a common and burdensome side-effect of GEP NETs that impacts functional and social wellbeing [6, 10, 15, 22]. Underlying causes of diarrhea can be multifactorial and include malabsorption of bile acids and fat due to surgical resection, SSA treatment, pancreatic insufficiency, or tumoral hypersecretion of serotonin (Fig. 1) [15].

Nutritional Issues in Patients with GEP NETs

Vitamin Deficiencies

Some studies have explored the potential impact of GEP NETs and their treatment on vitamin synthesis and absorption, with emerging data indicating a risk of niacin and fat-soluble vitamin deficiency in some patients [23–26]. These deficiencies can be a result of several factors

Table 2. Studies reporting symptom prevalence (%) in patients with GEP NET

Study	Diagnosis, sample size	Diarrhea, %	Steatorrhea, %	Fatigue, %	Food intolerance, %	Flushing, %	Abdominal pain/cramps, %	Weight loss, %	Appetite loss, %
Frojd et al. [19], 2007	Carcinoid tumor (*n* = 59)	50	–	69	–	53	50	–	39
Fiebrich et al. [24], 2010	Carcinoid tumor, on SSA (*n* = 35)	–	23	–	–	–	–	–	–
Haugland et al. [14], 2013	GI NET (*n* = 41)	35	–	35	89	19	–	–	–
Singh et al. [17], 2016	76% GI NET/pNET 12% lung NET (*n* = 1,928)	48	19	56	–	37	41	21	–
Lind et al. [26], 2016	SI NET, post-surgery (*n* = 50)	88–92	48	–	–	–	24–48	–	8–12
Borre et al. [48], 2018	66% GI NET/pNET 20% lung NET (*n* = 186)	27	–	–	–	–	22	–	–

GEP NET, gastroenteropancreatic neuroendocrine tumors; SSA, somatostatin analog; GI, gastrointestinal; pNET, pancreatic NET; SI, small intestinal.

Table 3. Symptoms associated with treatment modality [3, 6, 36]

Treatment	Potential side-effects
Surgery	
Pancreatic resection	Steatorrhea, nutrient malabsorption, hyperglycemia
Bowel resection	Diarrhea, steatorrhea, nutrient malabsorption, short gut syndrome, bacterial overgrowth, dehydration
Targeted therapy	
Everolimus	Diarrhea, fatigue, mucositis, hypothyroidism, nausea, hyerglycemia
Sunitinib	Diarrhea, fatigue, nausea, hypothyroidism, mucositis
SSA	Abdominal pain/cramps, nausea, constipation, pancreatic insufficiency, diarrhea, steatorrhea, fat malabsorption, fatigue
PRRT	Nausea, vomiting, pain (immediately post-treatment), carcinoid syndrome flare
Chemotherapy	Fatigue, nausea, vomiting, low appetite, diarrhea, constipation, mucositis

SSA, somatostatin analog; PRRT, peptide-receptor targeted therapy.

related to GEP NETs including depletion of internal stores or malabsorption related to serotonin hypersecretion, and treatment modalities including surgical resection and SSAs. Studies investigating the prevalence of vitamin deficiencies in patients with GEP NET are summarized in Table 4.

Niacin

Evidence is emerging on the impact of serotonin-producing NETs on niacin (vitamin B3) deficiency and risk of pellagra [23, 25]. In healthy individuals, niacin is synthesized from the amino-acid tryptophan [27]. In the presence of a NET, serotonin is synthesized preferentially to niacin, potentially leading to deficiency (Fig. 2) [23, 27–31].

The impact of over-production of serotonin on niacin status in people with NETs has been examined by several researches since the 1960s [29, 30, 32]. Previously it has been reported that between 5 and 20% of patients with serotonin-producing NETs or carcinoid syndrome present with clinical features of pellagra [32, 33]. The actual prevalence of biochemical or "sub-clinical niacin deficiency" may be as high as 30–45% [23]. Two studies have examined

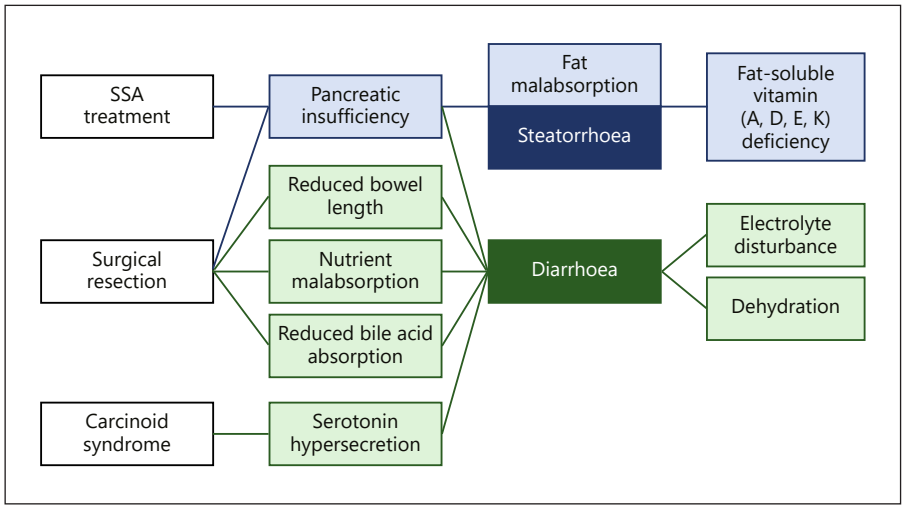

Fig. 1. Causes and impact of diarrhea in GEP NETs. Steatorrhoea, bowel disturbance characterized by pale, oily, and floating stools, often associated with diarrhea. SSA, somatostatin analog.

the prevalence of niacin deficiency in patients with GEP NETs (Table 4) [23, 25]. The first study by Shah et al. [23], conducted in the United States and Canada, found that 28% ($n = 36$) of NET patients newly diagnosed with carcinoid syndrome had serum niacin deficiency, whereas rates of deficiency in patients without carcinoid syndrome were significantly lower (13%, $p < 0.05$). A more recent study by Bouma et al. [25] reported that 45% of patients, diagnosed with "serotonin-producing" NETs had low niacin levels, as tested via 24-h urine samples. Each study utilized a different method of niacin analysis, thus complicating a clear comparison between results. Urinary excretion of N1-methyl nicotinamide and its derivative N1-methyl-2-pyridone-5-carboxyamide, used in Bouma's study, is the most reliable and sensitive measure of niacin status [34].

There is limited evidence to inform when patients are most at risk of niacin deficiency with research so far only providing prevalence data from small cross-sectional samples. The prevalence and impact of biochemical or sub-clinical niacin deficiency compared to symptomatic niacin deficiency (pellagra) also requires further exploration. Shah et al. [23] reported that of the 28% of patients diagnosed with serum niacin deficiency, only 1 patient had clinical signs of pellagra. This result is similar to previous documented rates of pellagra in NET patients [33]. Up to 80% of patients with carcinoid syndrome die soon after identification of pellagra, due to the advanced stage of their NET disease [32]. This indicates that niacin deficiency and risk of pellagra worsens over time and is potentially more prevalent in patients with a prolonged history of advanced NET. Diagnosis, through assessment of clinical symptoms, may potentially be too late to provide

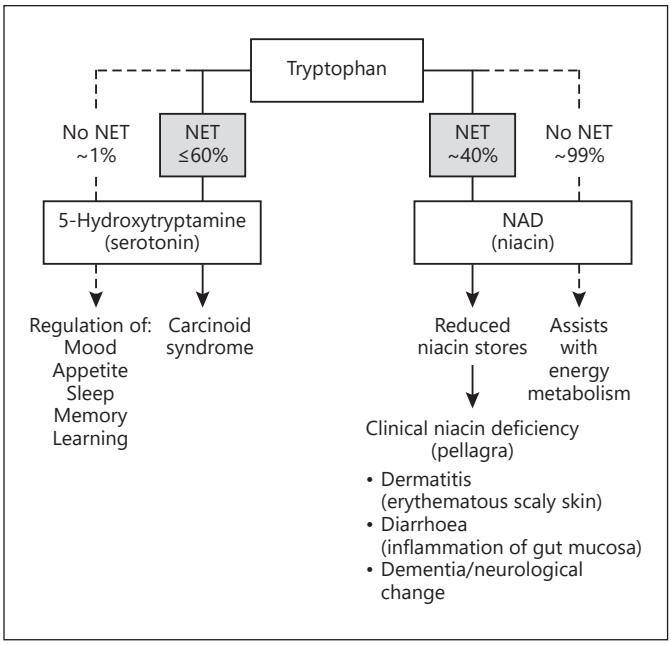

Fig. 2. Impact of NETs on niacin synthesis. NET, neuroendocrine tumor. NAD, nicotinamide adenine dinucleotide.

reversible treatment. Therefore, assessment of the underlying sub-clinical biochemical deficiency is crucial to reduce morbidity and risk of death from pellagra. Gastrointestinal symptoms of pellagra are similar to symptoms caused by the presence of a NET, and confusion regarding the cause of these symptoms risks diagnostic delay [27].

Niacin supplementation is an effective method to treat known deficiency [25]. Current best-practice guidelines

provide little guidance to clinicians on systematic testing and management of niacin deficiency. For the general population, the recommended daily intake of niacin proposed by the Australian National Health and Medical Research Council is 14–16 mg/day. The Carcinoid Cancer Foundation recommends 25–40 mg twice daily niacin supplement for carcinoid patients experiencing weight loss, poor appetite, carcinoid syndrome or who have undergone previous bowel resection [35]. In the article published by Bouma et al. [25], the mean daily niacin supplementation of patients with deficiency was 144 mg (range 3–300 mg), and supplementation in this study was reported to be effective to treat deficiency.

Interventional studies are thus required to test the optimal treatment of niacin deficiency, as well as the optimal dosing of niacin supplementation to prevent deficiency in at-risk patients. Based on current evidence it would be reasonable to recommend pro-active niacin supplementation (at least 40 mg/day) to patients with carcinoid syndrome, and at least 100 mg/day to patients with known niacin deficiency.

Fat-Soluble Vitamins

Diarrhea and steatorrhea are the direct side-effects of GEP NETs, as well as their surgical resection and SSA treatment; and may indicate an increased risk of excreting fat-soluble vitamins and thus subsequent deficiency [15]. SSA treatments have an anti-secretory effect by inhibiting secretion of bioactive peptides, hence reducing hormone-related symptoms. SSA treatment can, however; influence secretion of intestinal fluid, pancreatic enzymes, and bile acids, impacting nutrient digestion and absorption processes [3, 36, 37].

Results from studies testing serum fat-soluble vitamin levels in GEP-NET patients have been conflicting, and prior to 2010 scant research had examined this phenomenon [38]. All studies used a cross-sectional design in participants with varied demographics and presentations, and measured rates of vitamin D deficiency ranged between 31 and 81% (Table 4) [24, 26, 39–41]. Patients with GEP NET have been shown to have lower serum vitamin D than healthy controls [40]. One study by Fiebrich et al. [24] tested 35 patients with metastatic mid-gut NET, who were taking SSAs for >18 months, and found that 80% of patients had at least one fat-soluble vitamin deficiency. The median length of time on SSA treatment for subjects was 47 months, however, no correlation was found between the length of time on treatment and the risk of deficiency [24]. SSA treatment was also associated with a lower vitamin D level in a larger study by Massironi et al. [40]. In these studies, most subjects had undergone previous bowel surgery, which may have increased their risk of nutrient malabsorption. Studies by Lind et al. [26] and Fiebrich et al. [24] recorded use of pancreatic enzyme replacement therapy (PERT) amongst participants (14–28%). PERT promotes absorption of fatty acids in the small intestine and may play a role in addressing malabsorption and reversing the cause of fat-soluble vitamin deficiencies. Use of PERT is a confounding factor but was not taken into account during analysis of results in either study.

In contrast to previous studies, a study by Motylewska et al. [39] compared the prevalence of vitamin D between patients with a NET ($n = 32$) and a healthy control group. Rates of vitamin D deficiency did not differ significantly between groups (81 and 89%, respectively), but the rates overall were considerably higher than other studies, potentially due to the exclusion of patients taking vitamin D supplementation [39]. Factors relating to dietary intake as well as seasonal variations and geography must be considered when testing vitamin D levels. The Australian Bureau of Statistics has reported that 23% of Australians were classified as having a vitamin D deficiency in 2011–2012 [42], a prevalence which is considerably less than in the healthy control group recruited in Motylewska et al. [39]. All studies considered seasonal variations and recorded sun exposure of participants when testing vitamin D levels, but did not perform subanalysis on these factors to determine the extent of their contribution.

Overall, research to date examining rates of fat-soluble vitamin deficiencies in patients with NETs, has lacked a systematic approach and has focused on small heterogeneous patient groups. More information is needed to determine whether there is an increased risk of fat-soluble vitamin deficiency in NET patients compared to general populations. Up to 28% of patients with mid-gut NET have been documented to take PERT [24, 26, 43]; however, evidence for its effectiveness and the proportion of patients with NETs that benefit from PERT remains unclear. NET patients' post-small bowel resection and/or receiving SSA treatment should be screened for diarrhea and steatorrhea. In the presence of steatorrhea, PERT should be initiated, and symptoms closely monitored. In the absence of diarrhea, it is reasonable to consider testing fat-soluble vitamins through blood samples to monitor deficiency. Oral supplementation is effective in increasing serum vitamin D levels in NET patients [26, 40, 41], but evidence for the indication and effectiveness of other fat-soluble vitamin supplementation in NET patients is absent.

Table 4. Prevalence of vitamin deficiencies in GEP NET

Study	Vitamins tested	Testing method	Sample size, participant characteristics	Study design	Results			Existing vitamin use recorded
					niacin	vitamin D	other	
Shah et al. [23], 2005	Niacin	Blood sample	Newly diagnosed carcinoid, with carcinoid syndrome (CCS, $n = 36$) or without carcinoid syndrome (CCWS, $n = 32$), excluded patients on SSA treatment	Cross-sectional Control group ($n = 24$)	Niacin deficiency more common in CCS patients compared to controls (28 vs. 0%, $p < 0.05$)			No
Fiebrich et al. [24], 2010	Vitamins A, D, E, K	Blood sample	Metastatic midgut carcinoid tumor ($n = 35$), all treated with SSA >18 months	Cross-sectional No control group		31% vitamin D deficiency	80% low plasma level of at least 1 fat-soluble vitamin 32% >1 deficiency 69% vitamin K deficient	Yes
Bouma et al. [25], 2016	Niacin	24-h urine sample	Serotonin producing NET ($n = 42$), Grade 1 or 2, 50% small intestine NET, all had received niacin supplementation, 79% treated with SSA	Retrospective cohort, testing pre/post niacin supplementation Control group ($n = 133$)	Niacin levels lower in NET patients compared to health controls (pre-supplementation; $p < 0.0001$) 45% of NET patients had deficient niacin status pre-supplementation			Yes
Lind et al. [26], 2016	Vitamin D, B12	Blood sample	Disseminated small intestinal NET ($n = 25$), 98% undergone small bowel resection, 88% treated with SSA	Cross-sectional No control group		46% moderate/severe vitamin D deficiency 76% low bone density (DXA)	32% subnormal vitamin B12 ($n = 19$)	Yes
Motylewska et al. [39], 2016	Vitamin D	Blood sample	NET patients ($n = 36$), 64% GEP NET, 53% treated with SSA	Cross-sectional Control group ($n = 16$)		81% vitamin D deficient No statistically significant difference compared with healthy controls (89% controls vitamin D deficient)		Yes, excluded from analysis
Massironi et al. [40], 2017	Vitamin D	Blood sample	GEP NET ($n = 138$), 33% pNET, 25% functional symptoms, 79% previous surgery, 44% treated with SSA	Cross-sectional Control group ($n = 1,232$)		68% vitamin D deficient Patients on SSA had lower vitamin D ($p = 0.04$) GEP NET patients had lower median vitamin D than controls ($p < 0.0001$)		Yes, excluded from analysis
Robbins et al. [41], 2018	Vitamin D	Blood sample	GEP NET ($n = 183$), 62% previous surgery, 38% functional symptoms, 30% treated with SSA	Cross-sectional No control group		35.5% vitamin D deficient 31.3% vitamin D insufficiency		No

GEP NET, gastroenteropancreatic neuroendocrine tumor; SSA, somatostatin analog.

Malnutrition

Cancer-related malnutrition is associated with increased mortality, poorer QOL, increased healthcare costs, and reduced ability to cope with the demands of treatment [44, 45]. Patients with NETs are at risk of malnutrition due to various factors including the physical presence of cancer; paraneoplastic syndromes, disease or treatment-related symptoms; and malabsorption. Internationally, only 3 pilot studies have examined and reported on malnutrition risk or prevalence in patient's diagnosed with NETs. Overall their results have indicated that a quarter of NET patients are malnourished and up to 38% are at nutritional risk [46–48] (Table 5). All studies assessed malnutrition in a cross-sectional sample of NET patients and had similar sample sizes.

Qureshi et al. [46] found that 14% of GEP NET outpatients were at risk of malnutrition (MUST score ≥1) and a weak positive correlation between MUST score and treatment with SSA was found ($p = 0.013$). Maasberg et al. [47] assessed malnutrition in inpatients with varying types of NETs ($n = 203$) using the nutritional risk screening (NRS) score and the subjective global assessment (SGA) tool. Malnutrition was diagnosed in 25% of participants, with 21.7% diagnosed as being at "high risk of malnutrition" (NRS score ≥3) [47]. Borre et al. [48] also assessed nutrition risk in a cross-sectional cohort of NET patients, finding 38% scored high for nutritional risk (NRS score ≥3). The NRS is designed to predict the probability of health outcomes in an inpatient population due to nutritional factors, including whether nutritional treatment will influence outcomes [49]. Borre et al. [48] used the NRS in an

Table 5. Studies reporting malnutrition prevalence in NET

Study	Diagnosis, sample size	Setting	Study design	Nutritional status measure	Results
Qureshi et al. [46], 2016	GEP NETs, >40% mid-gut NET, 88.8% Grade 1 or 2 well-differentiated GEP NET (n = 161)	Outpatients	Cross-sectional	MUST	14% positive MUST score (>1) Weak positive correlation between MUST score and treatment with SSA (p = 0.013)
Maasberg et al. [47], 2017	33.5% mid-gut NET, 84.7% Grade 1 or 2 well-differentiated NET (n = 203)	87% inpatients	Cross-sectional	SGA, NRS	25.1% malnourished (SGA score B or C) 21.7% high risk of malnutrition (NRS score >3)
Borre et al. [48], 2018	66% GI NET/pNET, 92% Grade 1 or 2 (n = 186)	Outpatients	Cross-sectional	NRS, HGS	38% nutritional risk (NRS score >3) 25% low HGS

MUST, malnutrition universal screening tool; SGA, subjective global assessment; NRS, nutritional risk screening tool; HGS, hand grip strength; NET, neuroendocrine tumor.

outpatient population. Also, the NRS does not provide an assessment of malnutrition or the risk of a person being malnourished. Only Maasberg et al. [47] assessed the presence of malnutrition in NET patients using a validated assessment tool. The SGA has been validated for use in hospitalized patients and oncology populations to assess malnutrition; however, other tools exist that are more sensitive to subtle changes in nutritional status, specifically in people with cancer, including the patient-generated SGA [50].

These studies have demonstrated the existence and potential prevalence of malnutrition in people with a GEP NET; however, further research is required to determine individual or treatment-related factors associated with increase risk of malnutrition, and how it changes during the disease course. The proportion of patients with Grade 1 or 2 NETs was high in all studies (84.7–92%), potentially resulting in lower reported rates of malnutrition [47]. NETs histologically classified as Grade 1 or 2 are traditionally slower to progress and less aggressive in nature [51]; although on the contrary they are also more likely to have hormonal secretory syndromes and undergo bowel resection. Maasberg et al. [47] reported that patients with Grade 3 disease had a significantly higher prevalence of malnutrition than patients with Grade 1 or 2 disease (57.9 and 22.1% respectively, $p = 0.002$). As expected, patients with Grade 3 NETs, have aggressive and often more advanced disease and a greater preponderance to undergo treatment with chemotherapy. In the same study, patients with progressive disease of all grades and those receiving treatment with chemotherapy at the time of assessment also had higher prevalence rates of malnutrition, which was statistically significant [47]. Borre et al. [48] was the only study to assess patient-reported symptom burden and found that patients at nutritional risk (NRS ≥3) more frequently reported symptoms such as nausea, vomiting, stomach ache, and poor appetite.

Patients with GEP NETs who are malnourished are at higher risk of complications and mortality [47, 52]. Maasberg et al. [47] found that malnourished patients had significantly shorter overall survival (19.94 vs. 31.17 months, $p < 0.001$) and significantly longer length of stay than well-nourished patients (8.8 vs. 4.0 days respectively, $p < 0.001$). In a study by Glazer et al. [52], which analyzed data on 22,096 discharged NET patients using the United States nationwide inpatient sample database, malnutrition was associated with a higher risk of inpatient mortality (9 vs. 2%, $p < 0.0005$) and higher complication rate (15 vs. 10%, $p < 0.0005$). This study relied on classification of malnutrition via IDC-9 coding, therefore limiting detail available on the method of malnutrition diagnosis and other relevant patient data such as weight and BMI [52].

Thus all cancer patients should be screened for risk of malnutrition on diagnosis and during treatment, including patients diagnosed with a NET. The most appropriate nutrition interventions to address malnutrition in NET patients has not been studied, therefore interventional studies testing methods of nutrition therapy in NET patients is warranted.

Dietary Habits and Food Intolerance

Recent reviews have documented the importance of an individualized approach to nutrition management for patients with GEP NETs [11, 12, 38, 53]. In the absence of any symptoms, patients with a GEP NET are encouraged to follow healthy dietary guidelines as recommended for the general population [12, 38]. When symptoms are present and impact the function and QOL, there may be

a role for diet modification; however, there is limited research to guide interventions in this situation.

A large multinational survey conducted by Singh et al. [17] found that more than half of participants (n = 1,118, 58%) reported making dietary changes as a result of their NET. Food intolerance was reported by 89% (n = 33) of participants with a NET of the gastrointestinal tract in another study published in 2013, and was more frequently reported than other symptoms including diarrhea (n = 13, 35%) and fatigue (n = 13, 35%) [14]. These studies provide only limited data and type of food intolerance or dietary change and the actual rationale for the diagnosis of food intolerance was not explored. Nevertheless, it does highlight the considerable impact NETs can have on dietary intake and hence the potential relationship between symptoms and diet.

Only 4 published studies have reported data on dietary habits amongst patients with NETs [11, 26, 54, 55]. Studies by Gallo et al. [11] and Barrea et al. [55] have demonstrated that poor adherence to a Mediterranean style diet may correlate with increased NET severity or aggressiveness. The Mediterranean diet incorporates several healthy eating principles, including high fruit and vegetable intake and low saturated fat intake, considered optimal for good health and reduced disease burden. Only asymptomatic or disease-free patients with Grade 1 and 2 NETs were sampled for these studies and therefore results cannot be generalized to all NETs. Lind et al. [26] examined a small group of patients with mid-gut NETs and found that 36% (n = 9) reported to avoid either fermentable carbohydrates or fatty foods in an attempt to control symptoms of flatulence and diarrhea. In a qualitative study of 9 patients by Davies and Caplin [54], (published abstract), all patients reported restricting their diet and reducing meal sizes due to symptoms of their NET. Details of sampling approach, participant characteristics and methodology of some of these studies are limited, but results suggest that attention to diet and dietary habits are important to identify dietary restrictions which may impact the overall context of care for people with NETs. Patients with a NET, particularly those with carcinoid syndrome, are commonly misdiagnosed with other conditions such as irritable bowel syndrome, diverticular disease, food allergies or intolerances when presenting with generalized gastrointestinal symptoms such as diarrhea, abdominal discomfort, and pain [56]. Treatment for these conditions regularly involves dietary modification, which may be unnecessary or inappropriate if the underlying cause of these symptoms is due to a NET.

There is an absence of robust evidence regarding the dietary habits of patients with NETs and their impact on symptoms and QOL. The Carcinoid Cancer Foundation, a national non-profit organization in the United States, documented results on their website from a survey of NET patients (n = 97) in 1999, of which 43% had a small intestine NET and 79% had undergone intestinal resection [35]. Common dietary factors identified by these patients to trigger a reaction or "carcinoid crisis" (such as flushing or diarrhea) included eating a large meal, alcohol, tomato dishes, fatty foods, coffee/caffeine, chocolate, nuts, and spicy foods. In nutrition guidelines published online by The Carcinoid Cancer Foundation and other NET groups, patients with NETs are recommended to reduce consumption of foods containing amines, in an attempt to diminish symptoms of carcinoid syndrome [35]. There is currently no published evidence of a correlation between dietary amines and symptoms of carcinoid syndrome, and information at this stage remains anecdotal.

Nutrition within Clinical Guidelines

National and international clinical practice and consensus guidelines summarizing current evidence are available to clinicians and provide direction on diagnostic and medical aspects of NET patient care. These guidelines were developed by specialist professional groups including the North American Neuroendocrine Tumor Society, European Neuroendocrine Tumor Society and the European Society for Medical Oncology [1, 13, 37, 57, 58]. The importance of multidisciplinary collaboration and management of NETs is emphasized in some of these guidelines [1, 3, 5, 13]; this is mostly defined as a combination of various medical disciplines; such as medical oncology, surgical oncology, nuclear medicine, or endocrinology; specialized nursing input and links with NET patient support groups. The value of specialized nursing input and links with NET patient support groups is also highlighted in some clinical guidelines [6]. Regardless, the essential role of allied health professionals, such as dietitians and other clinicians providing supportive care has not been addressed or highlighted in NET research and guidelines. The majority of nutritional information available is online, from a range of sources, including public hospitals, NET support groups and organizations [35, 59–61], and appears to be based mostly on anecdotal evidence with limited published research available to support these recommendations.

Based on evidence available with regard to nutritional complications of GEP NETs, recommendations for clinical practice and suggestions for further research are summarized in Table 6.

Table 6. Summary of recommendations for nutrition management and further research

Nutrition complication	Recommendation	Suggested future research
Niacin deficiency	– Niacin supplementation is effective to treat deficiency – Consider supplementation (40–80 mg daily) in patients with carcinoid syndrome or high serotonin production – If deficiency known, supplement with at least 100 mg niacin per day – 24-h urine collection is the best method of testing, if available – Not useful to diagnose Pellagra based upon clinical symptoms alone and niacin testing is recommended to confirm it	– Interventional or randomized controlled trial is required to determine the most effective dose and method of niacin supplementation – Longitudinal prevalence studies looking at risk of niacin deficiency over time in patients with carcinoid syndrome
Fat-soluble vitamin deficiency	– If evidence of steatorrhoa commence PERT – Post small bowel resection, particularly if <200 cm small bowel remains, test for fat-soluble vitamin deficiency twice per year – Patients on fat-soluble vitamin supplementation may still require monitoring to ensure supplementation is effective – Consider testing fat-soluble vitamins twice per year in patients on long-term SSA >1 year	– Prospective research examining the effectiveness of PERT on the status of fat-soluble vitamins in NET patients – Comparison of vitamin D deficiency in NET patients versus the general population
Vitamin B12 deficiency	– Consider testing and supplementation post-stomach and small bowel resection – Supplementation via IV be more appropriate in patients with severe deficiency and major bowel resection	– Explore prevalence of deficiency through prospective cross-sectional and longitudinal studies, particularly post small bowel resection
Malnutrition	– All NET patients should be screened for risk of malnutrition at diagnosis, and at regular intervals during treatment – NET patients admitted to hospital, with high grade NET, progressive disease and undergoing chemotherapy are at greatest risk of malnutrition – Appropriate malnutrition screening tools include the MST, MUST and NRS – Assessment of nutritional status is best performed by a dietitian or other trained health professional using validated tools such as the PG-SGA	– Prospective longitudinal research is required to determine the change in nutritional status over time/ during treatment – Prevalence of malnutrition in NET outpatients should be established – Interventional studies testing the most appropriate method of nutrition therapy for malnutrition in NET patients
Dietary change and food intolerance	– Screen symptomatic NET patients for dietary changes and restrictions, as these are at risk of under-recognition – Food intolerances should not be assumed without thorough assessment from a NET dietitian and gastroenterologist – In some patients with carcinoid syndrome, foods containing high amounts of amines may exacerbate symptoms	– Prospective interventional studies testing the effectiveness of diet modification for symptom control – Prospective observational and interventional studies testing the impact of dietary amine consumption on the severity of carcinoid syndrome

PERT, pancreatic enzyme replacement therapy; NET, neuroendocrine tumor; SSA, somatostatin analogue; MST, malnutrition screening tool; MUST, malnutrition universal screening tool; NRS, nutrition risk screen; PG-SGA, patient generated subjective global assessment.

Conclusion and Recommendations

GEP NET are a heterogeneous group of tumors that have a distinct impact on patient's morbidity and QOL due to the tumor location, general effects of malignancy, hormonal hyper-secretion, and treatment. Malnutrition, vitamin deficiencies, and food intolerances are prevalent but currently under recognized in this population. If left untreated, these complications can significantly impact on patient's QOL, physical function, and survival. There are significant gaps in knowledge with regards to screening for malnutrition, dietary modification, and nutritional deficiencies in this patient group. Despite this, a validated tool should be used for malnutrition screening with all NET patients, and prophylactic supplementation and testing for vitamin deficiency in at-risk NET patients should be considered as part of standard care. Further large cross-sectional and longitudinal studies are required to better understand the nutritional impact of these complex tumors and to underpin the development of evidence-based nutrition guidelines for patients with GEP NETs.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

E.L. is a PhD student at The University of Melbourne, Australia. The authors indicate no other potential conflicts of interest.

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Author Contributions

E.L. conceived and designed the manuscript with assistance from M.K., M.M., and N.K. E.L. analyzed and interpreted the literature and drafted the manuscript. All authors revised it critically for important intellectual content, and approved the final version for submission.

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