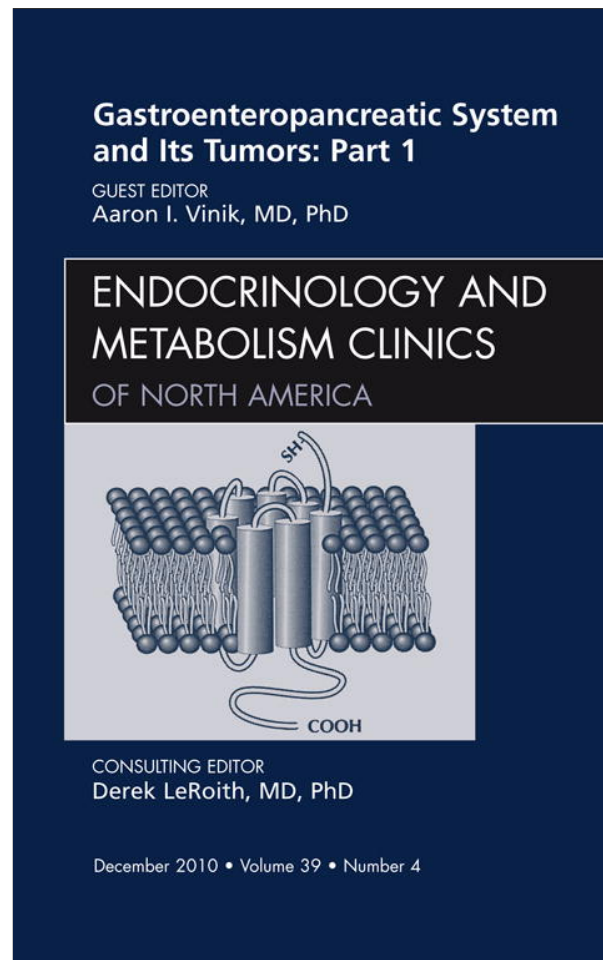


Provided for non-commercial research and education use.  
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>

# Nutrition and Gastroenteropancreatic Neuroendocrine Tumors

Vay Liang W. Go, MD<sup>a,\*</sup>, Priya Srihari<sup>b</sup>,  
Leigh Anne Kamerman Burns, MS, LDN, RD<sup>c</sup>

## KEYWORDS

• Diet • Nutrition • Metabolism • Neuroendocrine tumors

Gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) are relatively rare neoplasms that characteristically synthesize and secrete an excess of a variety of regulatory peptides, hormones, and neuroamines, which regulate gut and pancreatic function. This excess can lead to distinct clinical syndromes.<sup>1,2</sup> However, some GEP NETs are clinically silent until there are mass effects in their presentation with metastases. Therapeutic strategies include surgery, radiofrequency ablation, chemotherapy, chemoembolization, and biotherapy using somatostatin analogs.<sup>3,4</sup> The clinical syndromes and the various management strategies can lead to altered gut and pancreatic function with nutritional consequences. Nutritional and dietary management is critical for GEP NET patients and is the focus of this article.

## NEUROENDOCRINE REGULATION OF GUT-NUTRITION-METABOLISM AXIS

The gastrointestinal system plays an integral role in the assimilation of all nutrients from the diet. The macronutrients (carbohydrates, fats, and proteins) undergo digestion in the intestinal lumen by secreted enzymes from the pancreas and gut and in the brush-border surface for the intestinal mucosa. This is followed by absorption by enterocytes and subsequent transport of digestive products through the circulation. This entire process is highly regulated by the neuroendocrine system, including the autonomic nervous system, numerous gastrointestinal hormones, and regulatory

---

This work was supported by Grant No. AT003960 NCCAM from the National Institutes of Health.

The authors have nothing to disclose.

<sup>a</sup> UCLA Center for Excellence in Pancreatic Diseases, David Geffen School of Medicine at UCLA, 900 Veteran Avenue, Warren Hall 13-146, Los Angeles, CA 90095-1786, USA

<sup>b</sup> UCLA Center for Excellence in Pancreatic Diseases, David Geffen School of Medicine at UCLA, 900 Veteran Avenue, Warren Hall 13-146, Los Angeles, CA 90095-1786, USA

<sup>c</sup> Cancer Prevention Liaisons, LSUHSC School of Medicine New Orleans, Stanley S. Scott Cancer Center, 533 Bolivar Street, New Orleans, LA 70112-1249, USA

\* Corresponding author.

E-mail address: [vlwgo@ucla.edu](mailto:vlwgo@ucla.edu)

Endocrinol Metab Clin N Am 39 (2010) 827-837

doi:[10.1016/j.ecl.2010.08.003](https://doi.org/10.1016/j.ecl.2010.08.003)

0889-8529/10/\$ – see front matter © 2010 Elsevier Inc. All rights reserved.

[endo.theclinics.com](http://endo.theclinics.com)

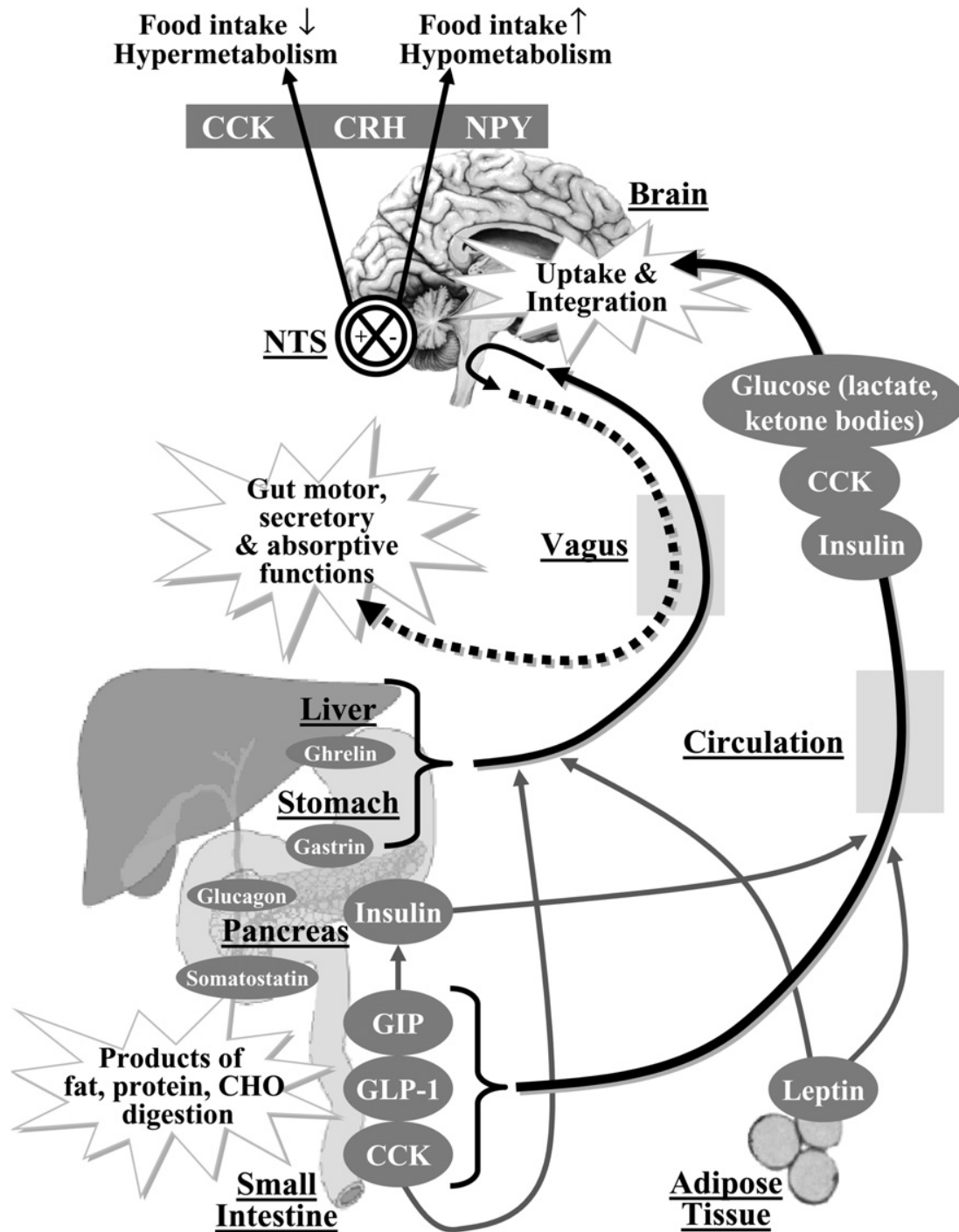
peptides, which act as paracrine, autocrine, and neurocrine pathways. Ingested food and absorbed nutrients provide well-coordinated gut functions including secretion, digestion, motility, and absorption.<sup>5</sup>

Neurohormonal regulation of gastric and pancreatic exocrine and endocrine secretion after a meal can be classified into the cephalic, gastric, and intestinal phases. The cephalic phase is initiated by sight, smell, taste, chewing, and swallowing of food and is mediated in the brainstem, posterior nucleus tractus solitarius, dorsal motor nucleus, and cortical nervous system. This phase activates vagal efferent impulses that stimulate both gastric and pancreatic secretion. The gastric phase occurs when food and fluids are present in the gastric lumen. Fifty percent of total acid secretion is stimulated by the meal. The greater the gastric distention, the greater is this acid secretion. The vagal nerve fibers mediate this phase and also regulate gastrin secretion. The intestinal phase is initiated by the entry of gastric chyme into the duodenum and the upper intestine. Quantitatively, this phase accounts for less than 10% of gastric acid secretion, but more importantly it regulates most of the pancreatic exocrine and endocrine secretion. This phase is primarily mediated by activating cholinergic reflexes and the release of gastrointestinal hormones, such as cholecystokinin (CCK), secretin, gastric inhibitory polypeptide, and glucagon-like peptide-1. These various hormones do regulate pancreatic endocrine secretions, insulin, glucagon, somatostatin, pancreatic polypeptide, and the secretion of digestive enzymes from the exocrine pancreas.

The various regions of the small intestine perform key digestive and absorptive functions. The duodenum and jejunum are the major sites of digestion and absorption of carbohydrates, proteins, and fats, and of absorption of most vitamins and minerals. Fat-soluble vitamins are integrated into the process of dietary lipid absorption, whereas water-soluble vitamins typically have their own mechanism for transport across the intestinal membrane. The ileum is the major site for absorption of water, electrolytes, and bile acids. The colon is the principal site of absorption of electrolytes and water. In addition, colonic bacteria provide the main source of short-chain fatty acids, such as acetate and butyrate. The transit of gastric and intestinal chymes is well coordinated by gastrointestinal motility, also under neurohormonal regulation.

The role of nutrients in the neurohormonal regulation of food intake and metabolism has been well documented (**Fig. 1**). Evidence now exists that nutrients have acquired a mechanistic and regulatory function in addition to the traditional concept of constituents of diet that serve as a significant energy-yielding substrate and as a precursor for the synthesis of macromolecules or components in normal cell differentiation, growth, renewal, and repair.<sup>5,6</sup> Nutrients could influence and regulate gene transcription, translation, and posttranslational metabolic processes. Moreover, they could regulate the release of gut neuroendocrine peptides that regulate motor, secretory, and absorptive functions, and the release of the metabolic hormone insulin. The neuropeptides released, such as CCK, could then act in both the circulation and vagal neural pathways, and interact with leptin peripherally in addition to its central action in regulate of satiety. In addition, leptin, being a long-term adiposity signal, may also increase the efficacy of CCK through interactions initiated at peripheral gastrointestinal sites or at dual sites with central leptin sensitizing the PVN to respond to inputs generated by the short-term satiety factor, CCK. The role of other gut neuropeptides on the peripheral actions of the neural vagal-sympathetic fibers need to be further investigated.

It is well established that neurohormonal pathways in the brain, gut, and adipose tissues play a key role in nutrient metabolism and fuel homeostasis, and it is also now established that nutrients (ie, glucose, free fatty acids, and amino acids) can



**Fig. 1.** The role of nutrients in the regulation of gut neuroendocrine system that activate vagal afferent fiber, interact with leptin synergistically to reduce food intake, and influence vagal efferent pathway to regulate gut motor, secretory, and absorptive functions. CCK, cholecystokinin; CHO, carbohydrate; CRH, corticotrophin-releasing hormone; GIP, gastrointestinal inhibitory peptide; GLP-1, glucagon-like peptide 1; NPY, neuropeptide Y; NTS, nucleus tract solitaries. (Modified from Go VLW, Wang Y, Yang H, et al. Neuro-hormonal integration of metabolism: challenges and opportunities in the postgenomic era. In: Allison SP, Go VLW, editors. Metabolic issues of clinical nutrition. Nestle Nutrition Workshop Series Clinical and Performance Program. Vevey/S. Kanger A.G. Basil 2004;9:227–42; with permission.)

regulate and modulate neurohormonal factors that affect metabolism at the cellular, organ-system, and whole-body levels. In this postgenomic era with genomic technology, this complex multiple nutrient metabolism and its control regulatory system can be analyzed simultaneously, from gene expression to metabolic flux to metabolic

phenotype affecting cell cycles and growth, development, and apoptosis, to quality of life and the dietary requirements of the individual.

### **NETS AFFECT GUT FUNCTION-METABOLISM**

Most NETs are small (<1 cm) and slow growing (months to years). They usually metastasize to the liver and bone before becoming symptomatic, often when the tumor is larger than 2 cm. NETs may have episodic expression and may be silent for years. They are often misdiagnosed, because their symptoms complex mimics other common disorders. Most GEP NETs are carcinoid tumors followed by insulinoma, pancreatic polypeptide, gastrinoma, VIPoma, glucagonoma, somatostatinoma, ghrelinoma, multiple endocrine neoplasia type I and type II, and other rare tumors.<sup>3</sup> Because of their rarity, for the most part endocrinologists make their living not by diagnosing and treating NETs, but rather by excluding disorders that masquerade as NETs. Perturbation of the gut's nutrition-metabolism process occurs in GEP NETs because of their excessive production of gastrointestinal hormones, peptides, and amines, which can lead to maldigestion, diarrhea, steatorrhea, and altered gastrointestinal motility that develops into various clinical syndromes (**Table 1**).<sup>3</sup> Gastrinoma, Zollinger-Ellison syndrome, is characterized by gastric hyperacidity caused by gastrin hypersecretion from islet cell tumors or the duodenum. Approximately 90% of gastrinomas are found in the "gastrinoma triangle," an area bordered by the confluence of the cystic and common ducts superiorly, the lateral sweep of the "C" loop of the duodenum, and the mesenteric vessels medially. The classic description of insulinoma is the Whipple triad, whose symptoms complex includes hypoglycemia with low blood glucose relieved by ingestion of glucose. Most insulinomas are benign and can be located anywhere within the pancreas. In contrast, ghrelinoma, caused by excessive production of ghrelin, a gastric hormone, can cause hyperglycemia, insulin deficiency or resistance, and intestinal dysmotility. Glucagonoma is characterized by skin rash, dermatosis, deep venous thrombosis, depression, and diarrhea. Somatostatinoma is caused by hypersecretion of somatostatin. The salient features of this tumor include diarrhea and steatorrhea; diabetes; cholelithiasis; and dysmotility and hypochlorhydria caused by the inhibitory effect of somatostatin on gastrointestinal secretion, motility, and gut and pancreatic hormone secretion. In some GEP NETs, multiple hormones or peptides are responsible for symptoms or multiple tumors involving several organs, such as in multiple endocrine neoplasia type I and type II, and can confound the clinical diagnosis of NETs. Any surgical approaches that remove or alter the anatomy of the gastrointestinal tract or biotherapy, such as the need for somatostatin analogs that suppress the secretion of gastrointestinal pancreatic hormones and function, can also lead to alteration of gastrointestinal secretory, motor, and absorptive functions. The tumor production of an excess of a variety of regulatory peptides, the surgical management, or biotherapy with synthetic somatostatin analogs could have both dietary and nutritional consequences.

### **DIETARY MANAGEMENT IN PATIENTS WITH NETS**

Because of the intricacy of the NET symptom complex before, during, and after patient therapy and the specific nutritional needs related to the course of NETs, a registered dietician should be part of the multidisciplinary health care team. Unfortunately, there are a limited number of registered dietitians and physicians who have expertise in the nutritional management of NETs. Currently, there are also no national dietary guidelines developed specifically for NETs. The pioneering work of Warner's "Nutritional Concerns for the Carcinoid Patient" in 2000 has led her to develop nutritional

guidelines for the carcinoid patient, available at the Carcinoid Cancer Foundation.<sup>7</sup> These guidelines were updated in 2009. This is one of the key resources related to the field. The objectives of nutrition management are to assist in the development of individualized nutrition care plans, to promote optimal nutritional status, and to evaluate the effectiveness of nutritional approaches, with an overall goal to improve the quality of life of the patient during therapy. The best diet for an NET patient largely depends on whether or not the patient is symptomatic, the stage of the disease, and the type of therapeutic management.

For patients with newly diagnosed NETs without symptoms, it is prudent to follow the healthy diet based on the Dietary Guidelines for Americans, 2005, for health promotion and chronic disease prevention including cancer (**Box 1**).<sup>8</sup> The United States Dietary Guidelines for Americans is the latest scientific evidence-based review in nutrition, and provides information and advice for choosing a nutritious diet, maintaining a healthy weight, achieving adequate exercise, and keeping foods safe to avoid food-borne illness. The recommendations are translated for implementation by the US Department of Agriculture Food Guidance in My Pyramid, which has been continuously updated (**Fig. 2**) with the DASH Eating Plan.<sup>9,10</sup> These recommendation guidelines are similar to those suggested by the American Cancer Society, World Health Organization, and other academic societies and institutes of medicine, including the American Institute for Cancer Research, which has published *The New American Plate Cookbook*, containing recipes for a healthy weight and a healthy life.<sup>11</sup> The healthy diet is primarily a plant-based diet, with 5 to 10 servings of fruits and vegetables and less animal protein, substituting beans and other legumes for protein instead. It also consists of low-fat or fat-free dairy; foods with a good source of healthy fats, such as nuts and seeds, which are low in saturated fat and contain no trans fatty acids; and whole grains as a source of carbohydrates. This diet also limits salt and refined sugar intake. Dietary supplements should also be avoided unless recommended by a physician. The 2005 Dietary Guidelines for Americans is currently being updated by the Department of Health and the US Department of Agriculture Advisory Committee for the 2010 Dietary Guidelines. Unfortunately, their anticipated report has not yet been released.<sup>12</sup>

Most GEP NET patients are cancer survivors, primarily because of the advancement of various therapeutic and diagnostic procedures. The quality of life related to dietary guidelines has received major interest. In recent studies conducted by the American Cancer Society, there have been three major recommendations for all cancer survivors regarding lifestyle: 150 minutes of moderate or strenuous physical activity or 60 minutes of strenuous activity per week, at least five servings of fruits and vegetables per day, and no smoking.<sup>13</sup> This study indicated that less than 5% of the surveyed survivors meet all three recommendations, but those who did observed a better health-related quality of life. Population-based studies have shown that approximately 48% to 74% are not meeting the recommended five servings a day of fruits and vegetables, whereas this particular study revealed that 80% to 85.2% of survivors were not meeting the five-a-day recommendation. Although there was a higher correlation with physical activity and better health-related quality of life, previous research has shown that in survivors of some cancers, eating five servings of fruits and vegetables is negatively associated with depression, which in turn is negatively associated with health-related quality of life. The Neuroendocrine Unit at the Eastern Virginia Medical School examined quality of life in a more exclusive group of patients with NETs. They developed the Norfolk Quality of Life Tool, a questionnaire of 72 questions that determined the domains that had a great impact on NET patient quality of life.<sup>14</sup> The resulting data were separated into the domains of physical functioning, respiratory, depression,

**Table 1**  
**The clinical presentations, syndromes, tumor types, sites, and hormones**

Clinical Presentation	Syndrome	Tumor Type	Sites	Hormones
Flushing	Carcinoid	Carcinoid	Gastric, mid, and foregut, pancreas/ foregut, adrenal medulla	Serotonin, substance P, NKA, TCT, PP, CGRP, VIP
Diarrhea	Carcinoid WDHHA ZE MCT PP	Carcinoid VIPoma Gastrinoma Medullary carcinoma PPoma	As above Pancreas, mast cells Pancreas, duodenum Thyroid, pancreas Pancreas	As above VIP Gastrin Calcitonin PP
Diarrhea/Steatorrhea	Somatostatin	Somatostatinoma, neurofibromatosis	Pancreas, duodenum, bleeding gastrointestinal tract	Somatostatin
Wheezing	Carcinoid	Carcinoid	Gut/pancreas, lung	Serotonin, substance P, chromogranin A
Dyspepsia, ulcer disease, low pH on endoscopy	ZE	Gastrinoma	Pancreas (85%), duodenum (15%)	Gastrin
Hypoglycemia	Whipple triad	Insulinoma Sarcomas Hepatoma	Pancreas Retroperitoneal Liver	Insulin IGF/binding protein IGF
Dermatitis	Sweet syndrome Pellagra	Glucagonoma Carcinoid	Pancreas Midgut	Glucagon Serotonin
Dementia	Sweet syndrome	Glucagonoma	Pancreas	Glucagon

Diabetes	Glucagonoma Somatostatin	Glucagonoma Somatostatinoma	Pancreas Pancreas	Glucagon Somatostatin
Deep venous thrombosis	Somatostatin	Somatostatinoma	Pancreas	Somatostatin
Steatorrhea	Somatostatin	Somatostatinoma	Pancreas	Somatostatin
Cholelithiasis/ neurofibromatosis	Somatostatin	Somatostatinoma	Pancreas	Somatostatin
Silent/liver metastases	PPoma	PPoma	Pancreas	PP
Acromegaly/ gigantism	Acromegaly	Neuroendocrine tumors	Pancreas	GH-RH
Cushing disease	Cushing	Neuroendocrine tumors	Pancreas	ACTH/CRF
Anorexia, nausea, vomiting	Hypercalcemia	Neuroendocrine tumors	Pancreas	PTHRP
Constipation, abdominal pain		VIPoma	Pancreas	VIP
Pigmentation		Neuroendocrine tumors	Pancreas	VIP
Postgastrectomy	Dumping, syncope, tachycardia, hypotension, borborygmus, explosive diarrhea, diaphoresis, mental confusion	None	Stomach/duodenum	Osmolarity, insulin, GLP

*Abbreviations:* ACTH, adrenocorticotrophic hormone; CGRP, calcitonin gene-related peptide; CRF, corticotropin-releasing factor; GH-RH, growth hormone-releasing hormone; GLP, glucagon-like peptide; IGF, insulin-like growth factor; MCT, medullary carcinoma of thyroid; NKA, neurokinin A; PP, pancreatic polypeptide; PTHRP, parathyroid hormone receptor; TCT, thyrocalcitonin; VIP, vasoactive intestinal polypeptide; WDHHA, watery diarrhea syndrome; ZE, Zollinger-Ellison syndrome.

*Data from* Mamikuniam G, Vinik AJ, O'Dorisio TM, Woltering EA, Go VLW. Neuroendocrine tumors, a comprehensive guide to diagnoses and management. 4th edition. California: Interscience Institute; 2009.

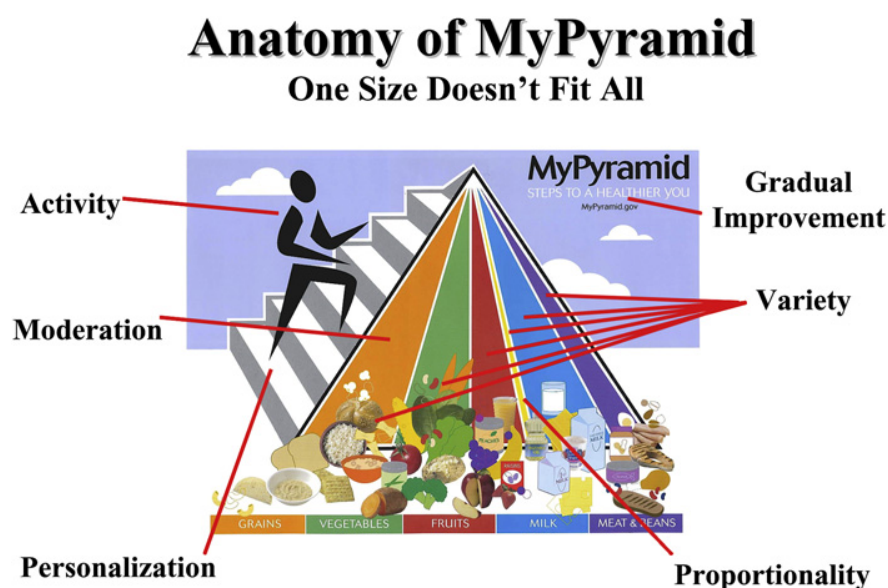
**Box 1****Recommendations by the 2005 Dietary Guidelines Advisory Committee**

- Monitor your body weight to achieve health
- Be physically active each day
- Choose a variety of foods with, and among, the basic food groups, while not exceeding your daily calorie limit
- Increase daily intake of fruits and vegetables, whole grains, and non-fat or low-fat milk and milk products
- Keep food safe to eat
- Decrease intake of saturated fat, trans fat, and cholesterol while increasing foods rich in omega-3 fatty acids (fish)
- Choose and prepare foods with less salt
- If you drink alcoholic beverages, do so in moderation

*From US Department of Health and Human Services, US Department of Agriculture. Dietary guidelines for Americans 2005. Washington: US Government Printing Office; 2005.*

cardiovascular, gastrointestinal, flushing, and positive or negative attitude. The questionnaire results further demonstrated that four particular domains were significant in NET patients: (1) physical functioning, (2) flushing, (3) gastrointestinal effects, and (4) depression. The nutrition and diet of patients can impact these domains.

Regarding the nutritional considerations for symptomatic NETs patients, it is advisable to follow the healthy diet plan recommended for nonsymptomatic patients, as described previously. However, every individual must weigh general advice against their own experience and symptoms complex. The most common symptoms complex includes diarrhea, abdominal pain, gas and bloating, and flushing. Lesser symptoms include fatigue, weakness, weight loss, and skin rash. There are some key nutritional



**Fig. 2.** Modified figure from the USDA Web-based food guidance system. (From MyPyramid.gov. US Department of Agriculture. Available at: <http://www.mypyramid.gov/index.html>. Updated March 24, 2010. Accessed April 27, 2010.)

issues to consider for this group of patients. They should avoid high amine-containing foods (**Box 2**). Avoiding spicy foods and alcoholic beverages may also help to prevent flushing.

There are several dietary substitutions that patients with NETs have learned can help their diarrhea. These include ripe bananas, pureed vegetables, and cooked or canned fruits, such as applesauce, instead of raw vegetables in the form of salad, fresh or dried fruit, pickles, and relishes. Rice, pasta, and potatoes can be substituted in place of high-fiber vegetables, such as cabbage. Other substitutions include jam or jelly on whole grain bread instead of cream cheese or butter on white bread; clear broth soup instead of creamy soup; crackers or pretzels in place of doughnuts and butter cookies; electrolyte replacement drinks, such as Gatorade, instead of carbonated soft drinks or fruit juice with pulp; and lactose-free beverages and products instead of regular milk and dairy products. It is important to determine whether the diarrhea is caused by the underlying endocrine tumors, such as VIPoma, gastrinoma, or carcinoid tumors, rather than other secretory diarrhea related to bacterial toxins, such as those in food poisoning, lactose intolerance, medications containing laxatives, or part of an irritable bowel syndrome. Loperamide or opiates have also been used for symptomatic improvement of NET-related diarrhea.

Currently, two somatostatin analogs, octreotide and lanreotide, are used to control symptoms of patients with NETs. Recently a multi-institutional German research group reported their results that the octreotide LAR significantly improves the time to progression among patients with metastatic, well-differentiated midgut NETs.<sup>15</sup> Their results also suggested the stabilizing effect of somatostatin analogs in NETs. Both synthetic somatostatin analogs are highly selective for somatostatin 2 receptors and have a prolonged plasma half-life with respect to somatostatin. Use of these

**Box 2****Amine-rich foods and products (tyramine, dopamine)****High**

- Aged cheeses (cheddar, Camembert, Stilton)
- Alcoholic beverages
- Smoked, salted, or pickled fish or meat (herring, salami, sausage, corned beef, bologna, pepperoni)
- Any spoiled protein foods (chicken liver)
- Yeast extracts and brewer's yeast, hydrolyzed proteins
- Broad beans, sauerkraut, shrimp paste, some soybean products, miso soup, soy sauce, tofu

**Moderately high**

- Caffeine-containing drinks, coffee (in large amounts), soda
- Chocolate (in large amounts)
- Some nuts (peanuts, coconuts, Brazil nuts)
- Some pizzas, raspberries, banana, avocado

*Data from Warner M. Nutritional concerns for the carcinoid patient: developing nutrition guidelines for persons with carcinoid disease. Carcinoid Cancer Foundation Web site. Available at: <http://carcinoid.org/pcf/lectures/docs/MwarnerlectureSept2.htm>. Updated 2009. Accessed April 6, 2010.*

analogs, which have all the biologic action of somatostatin in suppression of the gastrointestinal tract and pancreatic function, can lead to fat maldigestion and altered fat and fat-soluble vitamin absorption.<sup>16</sup> The adverse effects of somatostatin analog therapy are similar to those observed in somatostatinoma patients, which include steatorrhea, gas, nonspecific gastrointestinal discomfort, hyperglycemia, and hypothyroidism. Periodic monitoring of glucose metabolism, thyroid function, and plasma vitamins D and B<sub>12</sub> levels is recommended.

Systemic chemotherapy and combination therapy with somatostatin analogs, interferon, mTOR inhibitors, or vascular endothelial growth factor inhibitors are currently used. These therapies do have additional side effects including anorexia, weight loss, and liver function abnormalities.<sup>17,18</sup> Nutritional assessment and dietary changes need to be monitored and coordinated with the health care team.

There are other nutritional considerations in NET management. (1) Niacin deficiency can occur as a result of increased tryptophan metabolism into serotonin. This could lead to dermatitis, diarrhea, dementia, and death caused by pellagra. A daily supplement of 25 to 50 mg should be taken. (2) Another consideration is that pancreatic enzymes, such as pancrease, creon, and ultrase, are recommended for patients with steatorrhea, particularly related to somatostatin analog therapy. (3) Fat-soluble vitamins A, D, E, and K, and multiple vitamins are also advisable, particularly if the patient has fat malabsorption. (4) Maintaining an ideal body weight and preventing weight loss is important in monitoring the nutritional status of the patient. (5) In post-surgery patients, any alteration of gut anatomy can lead to malabsorption. Dietary changes and an appropriate nutritional care plan should be specifically developed for particular individuals. (6) Nutraceuticals or dietary supplements are used with caution. They may interfere with various chemotherapies, and there is a lack of evidence-based data to support their use.

## SUMMARY

Nutritional assessment and development of nutrition care plans are an integral part of the multidisciplinary management team for patients with NETs. Registered dietitians or physicians with expertise in nutrition can provide dietary approaches to improve the quality of life and nutritional status during various therapeutic modalities used in patients with NETs. They can monitor these patients and provide appropriate dietary changes to address the various side effects of therapy.

It is prudent to follow the Dietary Guidelines for Americans for health promotion and disease prevention including cancer. A prospective clinical trial focused on investigating nutritional status as a consequence of the course and various types of NETs is urgently needed to provide the appropriate database in the development of an evidence-based dietary guideline specifically for patients with NETs.

## REFERENCES

1. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumors. *Lancet Oncol* 2008;9(1):61–72.
2. Vinik AI, Silva MP, Woltering G, et al. Biochemical testing for neuroendocrine tumors. *Pancreas* 2009;38(8):876–89.
3. Mamikuniam G, Vinik AI, O'Dorisio TM, et al. Neuroendocrine tumors, a comprehensive guide to diagnoses and management. 4th edition. Los Angeles (CA): Interscience Institute; 2009.
4. Plockinger U, Rindi G, Arnold R, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumors. A consensus statement on behalf of

- the European Neuroendocrine Tumor Society (ENETS). *Neuroendocrinology* 2004;80:394–424.
5. Go VLW, Wang Y, Yang H, et al. Neuro-hormonal integration of metabolism: challenges and opportunities in the postgenomic era. In: Allison SP, Go VL, editors, *Metabolic issues of clinical nutrition. Nestle Nutrition Workshop Series Clinical and Performance Program*. Switzerland: Vevey/S. Karger A.G. Basel; 2004:9. p. 227–42.
  6. Go VLW, Wong DA, Wang Y, et al. Prevention: evidence-based medicine to genomic medicine. *J Nutr* 2004;134:3513S–6S.
  7. Warner M. Nutritional concerns for the carcinoid patient: developing nutrition guidelines for persons with carcinoid disease. Carcinoid Cancer Foundation Web site. Available at: <http://carcinoid.org/pcf/lectures/docs/MwarnerlectureSept2.htm>. Updated 2009. Accessed April 6, 2010.
  8. *Dietary Guidelines for Americans 2005*. Washington: US Government Printing Office: Dietary Guidelines Advisory Committee; US Department of Health and Human Services, US Department of Agriculture; 2005.
  9. MyPyramid.gov. US Department of Agriculture. Available at: <http://www.mypyramid.gov/index.html>. Updated March 24, 2010. Accessed April 27, 2010.
  10. Karanja NM, Obarzanek E, Lin P, et al. The DASH eating plan at 1,600-, 2,000-, 2,600-, and 3, 1000-calorie levels. *J Am Dent Assoc* 1999;8:S19–27.
  11. American Institute for Cancer Research. *The new American plate cookbook*. Berkeley (CA): University of California Press; 2005.
  12. *Dietary Guidelines for Americans Web Site*. Available at: <http://www.health.gov/dietaryguidelines/>. Updated October 8, 2009. Accessed May 5, 2010.
  13. Blanchard CM, Courneya KS, Stein K. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. *J Clin Oncol* 2008;26(13): 2198–204.
  14. Vinik E, Carlton CA, Silva MP, et al. Development of the Norfolk Quality of Life Tool for assessing patients with neuroendocrine tumors. *Pancreas* 2009;38(3): e87–95.
  15. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. *J Clin Oncol* 2009;27:4656–63.
  16. Öberg K, Kaltsas G, Ferone D, et al. Standards of care in neuroendocrine tumors: biotherapy. *Neuroendocrinology* 2009;90(2):209–13.
  17. Yao JC, Phan AT, Chang DZ, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low-to-intermediate grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol* 2008;26:4311–8.
  18. Yao JC, Phan A, Hoff PM, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol* 2008;26: 1316–23.