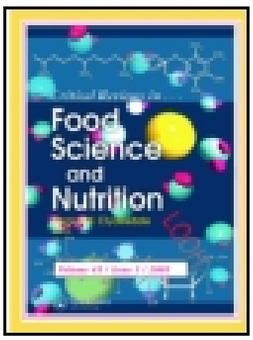

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Nutritional viewpoint of NETs

Narrative review

The management of neuroendocrine tumors: a nutritional viewpoint

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Abstract

Nutritional status in patients with neuroendocrine tumours (NETs), especially of gastroenteropancreatic origin, can be deeply affected by excessive production of gastrointestinal hormones, peptides, and amines, which can lead to malabsorption, diarrhoea, steatorrhea, and altered gastrointestinal motility. Besides, the surgical and/or medical management of NETs can lead to alteration of gastrointestinal secretory, motor, and absorptive functions, with both dietary and nutritional consequences. Indeed, disease-related malnutrition is a frequently encountered yet both underrecognized and understudied clinical phenomenon in patients with NETs, with substantial prognostic and socioeconomic consequences. Most of these conditions can be alleviated by a tailored nutritional approach, also with the aim of improving the efficacy of cancer treatments. In this setting, skilled nutritionists can play a fundamental role in the multidisciplinary health care team in NETs management and their presence should be recommended. The aim of this review is to provide dietary advices for each specific condition in patients with NETs, underlining the importance of a nutritional approach to treat malnutrition in this setting. Further, we will provide preliminary evidence coming from our data on the assessment of nutritional status in a single cohort of patients with NETs.

Keywords

neuroendocrine tumours, symptoms, nutrition, lifestyle, therapy

Introduction

Neuroendocrine tumors (NETs) include a heterogeneous group of tumours which are relatively infrequent, although an increased incidence and prevalence has been registered in the last years (Yao et al., 2008; Halfdanarson et al., 2008; Faggiano et al., 2012; Leoncini et al., 2017; Marciello et al., 2017). They affect the gastroenteropancreatic (GEP) system and the bronchial tract, but in rare cases they also occur in the ovaries, the urinary bladder, and other organs (Rindi and Wiedenmann, 2011). The most common sites of GEP NETs are represented by the small bowel, rectum, and pancreas (Dasari et al., 2017). NET-related symptoms are mostly due to the secretion of either gastroenteropancreatic hormones or biogenic amines (Rindi and Wiedenmann, 2011). In fact the clinical course of NETs can be characterized by various hormone hypersecretion syndromes such as the carcinoid syndrome or the hyperinsulinaemic hypoglycaemia syndrome of insulinomas (Pape et al., 2008). However, over 70% of patients have non-functioning NETs that never develop such a syndrome (Faggiano et al., 2012).

Disease-related malnutrition is a frequently encountered yet underecognized clinical phenomenon in patients with NETs, with substantial prognostic and socioeconomic implications both for affected patients and for caregivers. Clinically important endpoints such as quality of life or nutritional status have, however, been studied only very limitedly (Davies et al., 2006) or non-systematically (Marrache et al., 2007; Ekeblad et al., 2008). Body Mass Index (BMI) has been reported to reflect a poor nutritional status that could influence outcome in patients receiving transcatheter arterial chemoembolization (Marrache et al., 2007) or in patients with pancreatic NETs (Ekeblad et al., 2008).

The National Institute for Health and Care Excellence (NICE) recommends malnutrition screening in all adult inpatients and outpatients in at-risk groups (National Collaborating Centre 2006). One of the most used tool to assess malnutrition is the malabsorption universal screening tool (MUST) (BAPEN, 2015). However, the assessment of malnutrition in patients with GEP-NETs has been only reported in a single very recent study to date (Maasberg et al., 2017).

Currently, a comprehensive nutritional assessment of cancer patients is recommended and it is based on several methods such as the Subjective Global Assessment (SGA) (Detsky et al., 1984) or the Nutritional Risk Screening (NRS) (Kondrup et al., 2003), which now represent the most commonly applied nutritional status assessment tools in clinical practice. Anthropometric measurements include not only measurements of height and body weight, and the combination of both as the BMI, but also mid-upper arm circumference (MUAC) and triceps skinfold thickness (TST) as surrogates of malnutrition-associated loss of muscle mass or subcutaneous fat deposits (Frisancho, 1981).

Thus, the aim of this manuscript is to provide current evidence on NET related metabolism derangements and symptoms that could improve with an adequate nutritional management and to provide the best nutritional approach to treat malnutrition in this setting. Further, we will provide preliminary evidence coming from our data on the assessment of nutritional status in patients with NETs.

Nutrition and NETs

Similarly to other cancers, the overall goals of nutritional approaches for a NET patient is to develop individualized nutrition care plans, to promote optimal nutritional status, to evaluate the

effectiveness of nutritional interventions, and to improve the quality of life of the patient during therapy, depending also on whether or not the patient is symptomatic, the stage of the disease, and the type of therapeutic management. Thus, a skilled nutritionist should be part of the multidisciplinary health care team in NETs management, adapting the specific nutritional needs to the course of the disease. Despite the pioneering work of Warner's available at the Carcinoid Cancer Foundation (Warner, 2010), up to now there are no dietary guidelines specifically developed for NETs.

For patients with newly diagnosed asymptomatic NETs, it is useful to follow recommendations by the healthy diet based on the 2005 Dietary Guidelines Advisory Committee (DGA, 2005)(**Table 1**). However, due to the advancement of therapeutic and diagnostic procedures, most NET patients, mainly GEP-NET, are cancer survivors. According to the American Cancer Society the major nutritional recommendation for all cancer survivors regarding lifestyle is to eat at least five servings of fruits and vegetables per day (Blanchard et al., 2008). In general, patients with advanced cancer are often protein and fatty-acid deficient, with a close link with the decrease in skeletal muscle mass and weight loss (Murphy et al., 2010). Changes in food preferences and dietary habits are also commonly observed in advanced cancer, thereby exacerbating nutrient insufficiencies (Hutton et al., 2006). Sometimes, malnutrition due to cancer therapy toxicity (mucositis, candidiasis, and nausea associated with traditional chemotherapy) may worsen the nutritional status of the patient. In addition, nutritional status may directly affect both tolerance to and effectiveness of cancer treatments (Prado et al., 2008).

Specific nutritional advices should be taken into account for symptomatic NETs patients, in which the excessive hormonal production by the tumour led to syndrome-specific gastro-intestinal alterations (diarrhoea, malabsorption, nausea and vomiting, to mention a few) and metabolic disturbances (hyper or hypoglycaemia, dyslipidaemia), in addition to unspecific symptoms such as anorexia, weakness, and weight loss. Dietary advices for each specific condition are extensively reported in the following sections. An additional nutritional consideration in the management of patients with carcinoid syndrome is to supplement the intake of foods rich in niacin (Shah et al., 2005). The niacin deficiency, which can result from the increased tryptophan metabolism into serotonin, can lead to dermatitis, diarrhoea, dementia, and pellagra. Supplementation with niacin 25 to 50 mg/day is recommended (Go et al., 2010). Furthermore, pancreatic enzymes, such as pancrease, creon, and ultrase, and supplementations with fat-soluble vitamins A, D, E, and K, are particularly recommended for patients with fat malabsorption and steatorrhoea, particularly related to therapy with somatostatin analogues (SSAs)(Mamikuniam et al., 2009; Plöckinger et al., 2004). About the use of nutraceuticals or other dietary supplements there is scant evidence, and these products should be used with caution since they may interfere with anticancer agents.

There is considerable evidence that the Mediterranean diet (MD) represents a dietary pattern suitable for the prevention of non-communicable diseases, including cancer (Sofi et al., 2014). A meta-analysis including both cohort and case-control studies investigating the effects of adherence to MD on overall cancer risk evidenced that a high adherence to a MD is associated with a significant reduction in the risk of overall cancer mortality (10%), particularly from colorectal cancer (14%), prostate cancer (4%) and aerodigestive cancer (56%) (Schwingshackl

and Hoffmann, 2014). A few prospective cohort studies investigated the association between diet composition and cancer survival, reporting inconsistent results (Rock et al., 2012). For example, some studies focused on the evaluation of the relationship between survival and single nutrients rather than dietary patterns (Rock et al., 2012; Jones and Demark-Wahnefried, 2006). The beneficial effects of nutritional interventions promoting the Mediterranean food pattern could be extended to NET patients. Future well-designed dietary intervention trials on larger population samples are needed to define specific dietary guidelines for NETs.

Nutritional assessment of patients with NETs

There is convincing evidence that excess body fat is a cause of several cancers (Byers and Sedjo, 2015). Arnold et al. recently estimated that 3.6% of all incident cancers in the world in 2013 were caused by obesity (Arnold et al., 2015). It has been calculated that the increase in the risk of developing cancer for every 5 kg/m2 increase in BMI ranged from 9% to 56% (Kyrgiou et al., 2017). The BMI is inexpensive and easy to measure, and is considered a commonly used surrogate index for evaluating adiposity. Nevertheless, BMI evaluates excess body weight rather than excess body fat (Okorodudu et al., 2010), since it does not measure body fat directly and poorly distinguishes between fat mass and lean or bone mass (De Lorenzo et al., 2013). According to a recently published meta-analysis, BMI was the most relevant risk factor for NETs development at all investigated sites immediately after family history of cancer, and followed by diabetes (Leoncini et al., 2016).

Nevertheless, NET-related weight loss due to malnutrition is a frequently encountered yet under recognized clinical event, with relevant prognostic and socioeconomic implications both for

affected patients and for caregivers (Norman et al., 2008). Thus, waist circumference (WC) is recommended as an additional surrogate measure of fat distribution, due to its high correlation with visceral fat (Bosy-Westphal et al., 2010). A number of studies evidenced a strict association between WC and cancer incidence (Kyrgiou et al., 2017). In particular, WC has been associated with a higher risk of endometrial cancer indicating that central obesity, which is linked to hyperinsulinaemia and type 2 diabetes, has a major role in the development of this disease (Kyrgiou et al., 2017).

It is important to remind that the evaluation of the beneficial effect of therapeutic nutritional interventions should be monitored not only via the BMI, because this may be misleading in cases such as oedema (Maasberg et al., 2017). Bioelectrical Impedance Analysis (BIA) and its derived parameter Phase Angle (PhA) are non-invasive diagnostic tools widely used to evaluate body composition in different populations (Barbosa-Silva et al., 2005; Norman et al., 2012). BIA measures resistance to an electrical current and extrapolates fluid and fat compartments from this measurement (Barbosa-Silva et al., 2005; Norman et al., 2012). The parameters that can be measured include hydration status (intracellular, extracellular, and total water content), body fat mass, and electrolyte composition, which are essential in determining the overall health status (Grundmann et al., 2015). Malnutrition-associated patterns of body composition are increased Extra Cellular Mass (ECM), which is largely defined by extracellular water, and decreased Body Cell Mass (BCM) (Norman et al., 2012). The PhA is an indicator for cell membrane integrity, water distribution between the intra- and extracellular spaces and prediction of body cell mass, which is most commonly evaluated and correlated with nutritional status and survival rate (Paiva et al., 2010; Norman et al., 2010). Several studies indicate that the use of BIA and PhA measures

can aid in the clinical management of cancer patients (Grundmann et al., 2015; Haverkort et al., 2015).

The best use of BIA measurements is the evaluation of individuals over time to provide for longitudinal changes of PhA along with disease progression, nutritional interventions, and treatment. Very recently, we reported a novel association between the adherence to the MD and PhA, independently of sex, age, and body weight, recommending the nutrition assessment as good clinical practice in the evaluation of PhA in clinical settings (Barrea et al., 2017). Thus, BIA and PhA may be particularly useful also to evaluate and predict outcomes related to symptom management of patients with NETs, whose nutritional status and symptoms are clearly affected by their tumours. In particular, Maasberg et al. recently found significant differences in PhAs according to poorer nutritional status as assessed by BIA in NET patients, as reflected in a decreased PhA and an increased quotient of ECM to BCM (ECM/BCM index), indicating the loss of BCM and an increase in ECM (Maasberg et al., 2017).

Finally, the measurement of several circulating serum proteins such as albumin or transferrin as surrogates of protein turnover could also contribute to provide an overview of nutritional status (Gupta and Lis, 2010; Kyle et al., 2004).

In this context, skilled nutritionists can play a fundamental role in the multidisciplinary NET team and their presence should be recommended.

Gastroenterological symptoms

Diarrhoea and flushing

Chronic diarrhoea and flushing are among the most common clinical manifestations of functioning NETs. They usually occur in GEP NETs, the most common being carcinoids tumours, and in advanced (metastatic) disease (Kaltsas et al., 2004; Modlin et al., 2008).

Chronic diarrhoea is defined as loose stools occurring more than three times in one day and lasting for more than four weeks (Schiller et al., 2017). It occurs as a consequence of excessive production by the tumour of gastro-intestinal hormones, peptides and amines (serotonin, dopamine, histamine, vasoactive intestinal peptide (VIP), gastrin, glucagon, calcitonin and prostaglandins, among others), which affect gastro-intestinal (GI) functions (secretion, absorption and/or motility), leading to various clinical syndromes (Kaltsas et al., 2004; Modlin et al., 2008; Boutzios and Kaltsas, 2015) (**Table 2**). According to current characterization, chronic diarrhoea may be subdivided into different categories, which may overlap, by pathophysiology (e.g. secretory, malabsorptive, hypermotility forms, to mention a few) and by stool characteristics (e.g. watery or fatty) (Schiller et al., 2017). The majority of NETs patients are characterized as having a watery diarrhoea due to decreased net absorption of water by the intestine, the so-called secretory diarrhoea. Indeed, bioactive amines and peptide hormones, when produced in excess, stimulate excessive mucosal secretion of fluid from the intestine, leading to diarrhoea. In this type of diarrhoea intestinal fluid secretion is isotonic with plasma and the stool electrolyte composition is similar to that seen with cholera (Schiller et al., 2017). Neither there is structural damage nor inflammation. Secretory diarrhoea occurs independently of dietary intake: it may be postprandial, mostly after large and fatty meals, but it persists despite fasting and at night. Certain foods and beverages may trigger diarrhoea and/or flushing, as well as emotional and/or physical stress does (**Table 3**). In some GEP NETs (somatostatinomas and

less frequently gastrinomas), diarrhoea is associated to steatorrhea (i.e. the presence of large quantities of unabsorbed fat in the stool) due to fatty acid malabsorption (Kaltsas et al., 2004; Modlin et al., 2008). Also, certain substances, such as calcitonin and prostaglandins, may cause GI hypermotility and marked reduction in the transit time of colonic contents, further contributing to cancer-associated diarrhoea (Rambaud et al., 1988). Finally, beside the tumour production of an excess of bioactive substances, diarrhoea may be the consequence of surgical and/or medical therapies, so that also the management of the tumour can have nutritional implications. For instance, the surgical resection of the bowel causes a direct loss of absorptive surface and may also lead to either accelerated (e.g. post-vagotomy diarrhoea) or slowed (impaired motility causing bacterial overgrowth) GI transit, thereby predisposing to diarrhoea and steatorrhea (Schiller et al., 2017). SSAs, that offer the best therapeutic option for managing clinical symptoms in patients with GEP NETs, have well-known GI side effects (diarrhoea and steatorrhea, gallstones, constipation, gas and dismotility) caused by the inhibitory effect of somatostatin on GI and pancreatic functions (Chung, 2016). Systemic chemotherapy (streptozocin, platinum salts, 5-fluorouracil, irinotecan, temozolamide, and capecitibine, to mention a few) and combination therapy with interferon, mTOR (everolimus) or tyrosine-kinase (sunitimib, vandetanib and cabozantinib) inhibitors, that are currently used in NETs, have additional GI side effects including diarrhoea, anorexia and weight loss, nausea and vomiting, and liver function abnormalities (Stein et ak., 2010; Chung, 2016).

Currently, the SSAs octreotide, lanreotide and pasireotide are used to control symptoms (including diarrhoea and flushing) of patients with GEP NETs (Gut et al., 2017; Chung, 2016). However, a not negligible number of patients do not achieve adequate symptom relief with SSAs

alone, and new therapeutic options (i.e. telotristat ethyl) are under investigation (Kulke et al., 2017). In patients refractory to SSAs, as well as in patients who experience the GI side effects of SSAs, anti-motility agents (loperamide and opiates) may be used for symptomatic improvement of NETs-related diarrhoea (Gut et al., 2017). They should represent the initial therapy in patients with medullary thyroid cancer and diarrhoea (Schlumberger et al., 2012). Also non-dairy, multi-strain probiotics that contain bifidobacteria or lactobacillus strains may be of help. In patients complaining of steatorrhea, pancreatic enzyme replacement therapy should be prescribed to improve nutrients absorption.

In addition to medical therapies, dietary and nutritional intervention can improve GI discomfort, global health status and quality of life of symptomatic patients. There are several nutritional key points to consider for symptomatic NETs patients suffering from diarrhoea (Warner, 2009; Go et al., 2010). First, water and fluids intakes are crucial in such patients to prevent dehydration and revert electrolytes alterations (hypokalaemia). The recommended daily intake of water/fluids is at least two quarts per day. Potassium fluids and foods may also be a useful addition to the diet and in severe cases (i.e. VIPomas) electrolyte replacements should be provided. Alcoholic beverages, carbonates soft drinks, coffee and caffeine-containing drinks should be avoided or consumed sparingly, since they may trigger diarrhoea due to their amines content (**Table 3**). For the same reason, also "hot" spices and certain foods should be avoided to prevent diarrhoea and flushing as well (**Table 3**). However, the effects of amine-containing foods and beverages are dose related, and small amounts may not trigger reactions (severe reaction 10--25 mg tyramine per meal; moderate reaction 6--10 mg tyramine per meal) (Warner, 2009). Moreover, the types of foods/drinks that cause this reaction are individual in nature and the reaction may strongly

differ from patient to patient. It should be advisable each patient to record on a diary food intake and the symptoms experienced afterwards. The size of the meal and the fat content may also trigger symptoms such as diarrhoea, steatorrhea and flushing, likely via stimulation of gut hormones release. Large meals and high fatty foods should be avoided: symptomatic patients should eat little and often and keep a moderately low intake of fat, mostly if they are affected by steatorrhea. Regular milk and dairy products (cream, butter, cheese, whole milk yoghurt) should be replaced, at least in part, by non-fat or low-fat milk and milk products, as well as by lactose-free products.

There are also several nutritional advices concerning dietary sources of fibre, that may help the patient to better control diarrhoea. Even if the diet should be high in fruit, vegetables and grains (5 to 10 servings/day) as suggested in all cancer patients, symptomatic NETs patients should reduce insoluble fibre and increase soluble fibre in the diet. Also, they should favor cooked and peeled fruit and vegetables instead of raw vegetables, fresh and dried fruit and pickles; fruit juice "without bits" instead of pure fruit smoothies (**Table 4**) (Warner, 2009; Go et al., 2010).

Nutrition intervention may be useful also in preventing flushing, that is commonly associated to diarrhoea in patients suffering from carcinoids (typical and atypical forms), VIP-omas and medullary thyroid cancer. Cutaneous flushing, defined as a sensation of warmth accompanied by visible reddening of the skin, results from changes in cutaneous blood flow due to vasoactive substances secreted by the tumor (5-hydroxytryptamine, histamine, substance P, serotonin, catecholamines, prostaglandins, kallikrein, kinins, tachykinins, VIP, calcitonin) (Hannah-Shmouni et al., 2016). As well as diarrhoea, flushing in NETs may be triggered by certain foods

and beverages, via stimulation of gut hormones release or via amines-containing food (**Table 3**), as well as by any stimuli that increases adrenergic activity (physical and/or emotional stress, certain drugs) (Warner, 2009; Go et al., 2010).

Pyrosis

Gastrinoma is a rare GEP NET mainly arising from duodenum (75%) and pancreas (25%), which can be sporadic or occur as a component of the genetic disorder multiple endocrine neoplasia (MEN)-1 syndrome (20%-30% of cases). Excessive secretion of gastrin may cause the Zollinger-Ellison syndrome, with peptic ulcer disease and serious reflux oesophagitis. Gastric pyrosis, abdominal pain, and digestive disorders are the most important symptoms reported by patients with gastrinomas (Zhang et al., 2016). The first therapeutic approach is based on lifestyle change and on correct diet to reduce the acid secretion and control pyrosis. Obesity, smoking, alcohol abuse and diet are the most important factors involved in acid secretion control. In addiction high dietary fibre intake and moderate physical activity seem to improve symptoms (Ness-Jensen et al., 2016; Kaltenbach et al., 2006).

In general:

- Weight reduction in obese or overweight patients can reduce acid exposure;
- Tobacco smoking cessation will normalize the lower oesophageal sphincter pressure and salivary bicarbonate production;
- Alcohol consumption may increase acid secretion through gastrin stimulation;

- Avoidance of foods that may precipitate acid secretion, such us coffee, chocolate, peppermint, citrus, carbonated drinks, spicy and fatty food (Ness-Jensen et al., 2016; Kaltenbach et al., 2006).

Constipation

Constipation is medically defined as less than three bowel moments per week and is considered severe if a person has less than one bowel movement per week. Symptoms of bloating and gas may accompany constipation (Anthony, 2010). Constipation is a less common condition than diarrhoea in NETs patients. Most of times it occurs in non-functioning GEP NETs as a consequence of intestinal obstruction by the tumour mass or represents a side effect of medical therapies of either functioning or non-functioning NETs (SSAs, chemotherapy, everolimus, sunitinib) (Kaltsas et al., 2004; Modlin et al., 2008; Chung, 2016). Noteworthy, longstanding constipation is a rare complication of phaeochromocytoma and paraganglioma. The hypersecretion of catecholamines by the tumor may reduce the peristaltic activity of the gastrointestinal tract, resulting in chronic constipation and intestinal pseudo-obstruction (Thosani et al., 2015).

In NETs patients with chronic constipation nutritional and dietary intervention are aimed to prevent dehydration and help bowel movements. Water/fluids intake should be increased over the normal habit of the patient and high fibre diet should be followed (whole grains, vegetables and fruit with high fibre content), avoiding gas-forming foods (e.g. onions, garlic, cabbage, pulses, cauliflower, broccoli, nuts) (**Table 5**). Regular and moderate physical activity/gentle

exercise may also help regulate bowel motility. Stimulant laxatives, including herbal products, should be used as a last resort (Warner, 2009).

Metabolic effects

Hypoglycaemia

Hypoglycaemia is the distinctive feature of insulinoma, the most common functioning NET of the pancreas, with an annual estimated incidence of 1--4 per million population (de Herder et al., 2006; Shin et al., 2010). Approximately 90% of insulinomas are solitary, more than 90% are benign, and 5–10% are associated with MEN-1. Causing intermittent oversecretion of insulin, insulinomas classically present with recurrent episodes of spontaneous hypoglycaemia. Early recognition and diagnosis are often challenging. Historically, diagnostic workflow starts from the presence of Whipple's triad, which includes: 1) symptoms and/or signs of hypoglycaemia; 2) low plasma glucose ($\leq$ 2.2 mmol/L; $\leq$ 40 mg/dL); 3) recovery of symptoms and/or signs after administration of glucose.

Glucose is an obligate metabolic fuel for the brain, and a virtually continuous supply of glucose from the circulation is fundamental for survival. Since blood-to brain glucose transport is a direct function of blood glucose concentration, prolonged or profound hypoglycaemias can produce important metabolic derangements and be life-threatening. Generally, symptoms of hypoglycaemia are categorized as either neuroglycopenic or neurogenic (**Table 6**).

When technically feasible, complete surgical excision is the treatment of choice. However, for patients who are not candidates for surgical resection (eg, malignant insulinomas with

unresectable metastatic disease) or those who are awaiting surgery, dietary modification designed to prevent prolonged periods of fasting becomes of paramount importance in the management of insulinomas.

There is little evidence about the best dietary strategy for people with insulinoma, and nutritional advice is mainly based on trust in the expertise. Most of the available studies deal with the management of hyperinsulinemic hypoglycaemia after bariatric surgery or postoperative dumping syndrome. However, in these patients, oversecretion of insulin is triggered by rapid absorption of glucose and is reactive to the ingestion of a meal, whereas insulin production is completely autonomous in patients with insulinoma.

The goal of dietary therapy is to prevent prolonged periods of fasting by consuming small, frequent meals throughout the day and night. Unless a body weight reduction is needed, a diet of adequate calories (30 Kcal/kg) consisting of a high protein, variable fat, and low carbohydrate content has proved satisfactory. Such a diet should be administered in regulated frequent feedings (splitting food intake into five to six light-meals), since shortening the number of hours between feedings is perhaps more important than the composition of the diet (dePeyster and Gilchrist, 1954; Kandaswamy et al., 2016). A high protein diet provides a source of glucose that may be metabolized over a prolonged period and causes a slow release of glucose into the bloodstream, thus reducing secondary hypoglycaemia from reactive insulin stimulation. Furthermore, it can prevent weight gain and obesity which is another typical manifestation of insulinomas, since patients eat frequently to prevent symptoms of hypoglycaemias. Low glycaemic index and complex carbohydrates can help maintaining blood glucose levels for

longer, reduce the glycaemic load, and therefore the symptoms of postprandial hypoglycaemia. Alcohol consumption should be avoided, since it reduces hepatic glucose production. In some circumstances, partial or total parenteral nutrition may become necessary, to the detriment of a major effect on daily life.

During hypoglycaemic episodes, oral administration of rapidly absorbable forms of carbohydrates with a high glycaemic index such as fruit juices, soft drinks, milk with added sucrose, candies or other snacks, or glucose tablets, are suited (up to 15--30 g of glucose), whereas parenteral glucagon or intravenous dextrose infusions are needed for the emergency treatment of hypoglycaemic coma, or when the patient is unwilling or unable to take carbohydrates orally. However, according to preliminary evidence from animal models, posttreatment hyperglycaemia after an episode of profound hypoglycaemia may contribute to neuronal damage and should be avoided (Cryer et al., 2009).

Hyperglycaemia

Varying degrees of imbalance of glucose metabolism up to overt DM with symptomatic hyperglycaemia may develop secondary to NETs, especially in patients with underlying genetic diabetic predisposition (Resmini et al., 2009; Minuto et al., 2014). Hyperglycaemia may result from: a) a direct tumour mass effect on the pancreas, reducing insulin production; b) surgical treatment (total or partial pancreatectomy); c) overproduction of substances interfering with insulin secretion (e.g. catecholamines, somatostatin, or hypokalemia) and/or action (e.g. glucagon, glucocorticoids, catecholamines, ghrelin, or growth hormone), as in patients with pheochromocytoma, VIPoma, glucagonoma, somatostatinoma, or with paraneoplastic syndrome;

d) altered counterbalance between glycoactive hormones due to medical therapy (somatostatin analogues, interferon, steroids given with traditional chemotherapy, and/or everolimus)(Gallo et al., 2017).

Paradoxically, considerable improvements in treatment strategies, and consequently in life expectancy, have increased the number of patients with NETs developing diabetes and even diabetic complications, thus emphasizing the importance of appropriated diabetes management also in this setting.

Malnutrition is very commonly seen in cancer patients (and in patients with NETs), being responsible for an excess of morbidity and mortality, negatively influencing the outcomes of oncologic treatments, and worsening the quality of life (Norman et al., 2008). Malnourished patients should timely receive nutritional assessment and support, independently from the presence of DM and glucose control.

For people who are not losing weight, have symptoms controlled, are otherwise well, and have a long life-expectancy, a healthy balanced diet has an integral role in overall diabetes management, just like in every patient with DM (Royal Free London NHS Foundation Trust, 2014; American Diabetes Association, 2017; Evert et al., 2004). Since there is not a one-size-fits-all eating pattern for all individuals with DM, every patient should receive individualized medical nutrition therapy with the following goals: 1) to achieve and maintain bodyweight goals; 2) to attain individualized glycaemic, blood pressure, and lipid goals; and 3) to delay or prevent diabetes complications. Furthermore, appropriated advices should be given in order to maintain the pleasure of eating and to address individual needs based on personal and cultural preferences. In

overweight and obese patients a sustained reduction ≥ 5--7% of initial body weight, to be attained with dietary programs achieving a 500--750 kcal/day energy deficit, has been shown to be adequate.

As a general approach, healthful eating patterns containing nutrient-dense, high quality foods (such as whole grains, vegetables, fruits, legumes, low-fat dairy, lean meats, nuts, and seeds) in appropriate portion sizes should be emphasized, with less focus on specific nutrients or single foods. Indeed, studies examining the ideal amounts of daily carbohydrate, protein, and fats intake for people with DM are rather inconclusive.

In general:

- Monitoring carbohydrate intake and considering the blood glucose response to dietary carbohydrate (glycaemic index and glycaemic load) improve postprandial glucose levels;
- Replacing refined carbohydrates and added sugars with whole grains, legumes, vegetables, and fruits should be encouraged;
- Sugar sweetened beverages and foods with added sugars should be strongly discouraged;
- Protein intake should be individualized based on current eating patterns, taking into account kidney function;
- Trans fats should be avoided;
- Foods rich in long-chain ω-3 fatty acids are recommended to prevent or treat cardiovascular disease;

- Alcohol consumption should be moderated (≤ 1 drink/day for adult women, ≤ 2 drinks/day for adult men);
- Sodium consumption should be limited to < 2,300 mg/day.

Among healthful eating patterns, a Mediterranean-style diet rich in monounsaturated fatty acids (predominantly from olive oil), fruits, vegetable, whole-grains, and fish, is associated with a high degree of satiety, can improve both glycaemic control and blood lipids, and delay the need for antihyperglycaemic drug therapy (Esposito et al., 2009).

Lipids

High cholesterol levels have been detected in patients with cancer, due to the tumour per se or as a consequence of cancer therapy (Ray and Husain, 2001; Qadir and Malik, 2008; Utsumi et al., 2007; Namiki et al., 2007).

There is little evidence on the association between NETs and dyslipidaemia. Everolimus is currently used for the treatment of NETs. An increase of total cholesterol with everolimus has been reported by several studies (Baur et al., 2011; Brattstron et al., 1998). Treatment with everolimus is also associated with a significant increase of plasma triglycerides (Lorber et al., 2005; Vitko et al., 2004). This association could be explained by the fact that mTOR Complex 1 (mTORC1) controls lipid metabolism by different ways. Several data indicate that mTORC1 increases the activity of the transcription factor sterol regulatory element-binding protein-1c (SREBP-1c), upregulating the expression of enzymes involved in lipogenesis (acetyl-CoA carboxylase, fatty acid synthase, and stearoyl-CoA desaturase). It has been shown that

impairment of mTORC1 activity with rapamycin blocks the SREBP-1c induced expression of lipogenic enzymes. mTORC1 has been shown to increase PPARgamma expression, to promote adipogenesis (Zhang et al., 2009), and to increase the activity of lipin 1, which is a phosphatidic acid phosphatase promoting triglyceride synthesis and enhancing the PPARgamma adipogenic activity. Some traditional chemotherapy agents also alter lipid profile: e.g., doxorubicin can reduce high density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (apoA1) levels, and rise apolipoprotein B (apoB) levels, probably via a reduced expression of the ATP binding cassette transporter A1 (ABCA1) in liver cells through downregulation of the liver X receptor α (LXRα) and peroxisomal proliferator activated receptor γ (PPARγ) transcription factors (Sharma et al., 2016).

Therefore the assessment of lipid profile is of paramount importance in patients with NETs treated with everolimus. In fact an early diagnosis of dyslipidaemia could allow a personalized nutritional approach contributing to reduce the increased cardiovascular risk.

Foods to avoid for patients preparing for the 24-h urine 5HIAA test

Preparing for the 24-hour urine 5HIAA test some medication as some drugs that can interfere with 5HIAA measurements should be discontinued (eg, cough syrup and reserpine, levodopa, MAO inhibitors, methyldopa, phenothiazines, and tricyclic antidepressants). Similarly, foods containing 5-hydroxytryptamine (serotonin), the precursor of 5HIAA, should be avoided for three days before the test and whilst collecting the sample of urine (see **Table 7**).

Nutritional habits among a single cohort of patients with GEP NETs

Shown below, we report the metabolic and diet profile of a single cohort of patients with GEP-NETs, followed up at the Neuroendocrine Tumors Unit of the "Federico II" University of Naples and who participated to a dedicated nutritional survey.

Functioning GEP NETs were not included with the aim to eliminate the potential confounding effect of functioning tumours (eg, insulinomas) on metabolic variables. Among the 50 patients with sporadic non-functioning GEP NETs, 37 entered this study. Five patients were excluded for insufficient data available, 2 patients were cachectic at time of first visit, and 6 patients were older than 70 years.

The diagnosis of GEP NET was histologically documented for all patients and defined according to the 2010 WHO classification criteria. Staging was defined according to the TNM system updated to 2010 (Bosman, 2010).

Clinical characteristics such as weight, height, WC, arterial blood pressure, dietary pattern, and metabolic parameters were evaluated at time of diagnosis of the GEP NET.

Metabolic Syndrome was defined according to the revised Adults Treatment Panel (2001), and three or more criteria were considered: plasma glucose concentration ≥100 mg/dL, WC > 88 cm, serum high-density lipoprotein (HDL) concentration < 50 mg/dL, blood pressure ≥130/85 mmHg, and serum triglyceride concentration ≥150 mg/dL.

A validated 14-item questionnaire for the assessment of adherence to the Mediterranean diet (PREDIMED) was recorded for all the enrolled subjects. Briefly, for each item a score of 1 or 0

was assigned; PREDIMED score was calculated as follows: 0–5, lowest adherence; score 6–9, average adherence; score ≥10, highest adherence (Martínez-González et al.,2012).

Therefore, the patients completed a 7 days diary to evaluate macronutrients distribution and diet composition.

Metabolic parameters evaluated were: fasting plasma glucose, serum total cholesterol, serum low-density lipoprotein (LDL) and HDL cholesterol, serum triglycerides, selenium, retinol, tocopherol and vitamin C levels.

In our group, a G1 NET diagnosis was reported in 20 patients (54%) and G2 in 17 (46%). Disease progression was reported in 5.4% of patients during the follow up, and 89,9% of them were treated with somatostatin analogues. Sporadic tumors were reported in 51.3% of the cases, and 48.7% had a diagnosis of MEN-1. Metastatic status was reported in 27% of patients, at time of diagnosis. The anthropometric and metabolic profile of the cohort are reported in **Table 8**.

In our cohort, 27% of the patients presented a good adherence to the Mediterranean diet, 56% a moderate adherence, and 16.2% a poor adherence. A poor vitamin (Ascorbic acid 78.4±48.4 mg) and selenium (23.8±14.8 mcg) status were registered, relative to standard values.

Subjects with high blood pressure presented higher levels of Ki-67 index (5.0±5.6 vs 3.7±2.6; $p = 0.004$), and a higher tumor size at diagnosis was reported in patients with diabetes (2.3±4.1 vs 0,85±1.3; $p<0.001$). A correlation analysis was performed: a positive association between tumor size and total and LDL cholesterol levels was reported ($r = 0.419$, $p<0.001$; $r = 0.498$, $p = 0.002$; respectively).

No significant differences were reported about diet composition in presence or absence of metastases at diagnosis (**Table 9**). In addition, we compared the diet composition between subjects with sporadic GEP NETs and MEN1 patients: no significant differences were seen, except for selenium levels (17.2±7.1 vs 30.7±17.9, p = 0.005).

Overweight and obesity were very common in our cohort of patients with GEP NETs (40.6% and 28.1% of patients, respectively). Furthermore, hypertension and diabetes were reported in 40.5% and 25% of the patients, respectively. Therefore we can conclude that a metabolic disease was very common in our patients with non-functioning GEP NETs, at diagnosis. In particular, metabolic disorders were associated with markers of disease severity: Ki-67 index was higher in patients with high blood pressure, and a greater tumor size at diagnosis was reported in subjects with diabetes. Lastly a positive association was observed between total and LDL cholesterol with tumor size. These data suggest that metabolic syndrome may associate with NET greater severity. The largest part of our group presented a medium grade of adherence to the Mediterranean diet, albeit we did not observe any difference relative to the presence of metastases or the hereditariness of the disease (sporadic vs MEN-1).

In conclusion, these preliminary data suggest that the metabolic profile may correlate with disease severity. In this context, a cooperation between Endocrinologists, Oncologists, and Nutritionists can represent an innovative and important approach to improve the follow up and prognosis of patients with GEP NETs.

Conclusions

NETs are characterized by symptoms that are related to the tumor *per se* but also to anticancer drugs. Most of these symptoms such as diarrhoea, flushing, pyrosis, and constipation can be alleviated by a tailored nutritional approach. A nutritional treatment could be also of paramount importance in the management of metabolic complications represented by hypo/hyperglycaemia and dyslipidemia. Thus, the nutritional counselling is mandatory before and during cancer treatments in patients with NETs in order to identify the best nutritional approach that not only will improve the symptoms but also contribute to make anticancer therapy successful.

Compliance with Ethical Standards

Funding: none

Conflict of Interest: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Table 1. Recommendations by the 2005 Dietary Guidelines Advisory Committee

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

Table 2

TUMOR	SECRETION PRODUCT/ BIOCHEMICAL MARKER	DIARRHOEAL SYMPTOMS	ASSOCIATED SYMPTOMS AND SIGNS
GEP- NET			
MIDGUT TUMOURS			
Carcinoid *(carcinoid syndrome)*	serotonin and tachykinins/ 24 hours urinary 5-hydroxyndoleacetic acid (5-HIAA), the primary catabolic product of serotonin	Chronic secretory watery diarrhoea after eating. It may be triggered by certain foods or alcohol and persists even during fasting and at night.	Flushing, wheezing and bronchoconstriction, sweating, weight loss, hypertension, right heart disease
FOREGUT TUMOURS			
VIPoma *(Verner-Morrison syndrome)*	vasointestinal peptide (VIP)/ serum VIP	Chronic secretory watery diarrhoea with excessive loss of water and electrolytes. Diarrhoea is really profuse and occurs even during fasting and night-time.	Dehydration, marked hypokalaemia, achlorhydria, acid-base disturbances, weight loss, flushing, hypotension.
Gastrinoma *(Zollinger-Ellison syndrome)*	Gastrin/ Serum gastrin and gastric pH	Chronic or intermittent secretory diarrhoea, with or without steatorrhea. It is responsive to proton-pump inhibitors	hyperchlorhydria, heartburn, nausea and vomiting, severe peptic ulceration, weight loss
Glucagonoma	Glucagon/ Serum glucagon	Chronic or intermittent secretory diarrhoea (in less than 15% of patients)	Necrolytic migratory erythema, stomatitis, weight loss, diabetes mellitus
Somatostatinoma	Somatostatin/ Serum somatostatin	diarrhoea and steatorrhea	gallbladder dysfunction and gallstones (cholelitiasis), weight loss, impaired glucose tolerance/diabetes mellitus
NON–GEP NET			
Medullary Thyroid Cancer	Calcitonin, Prostaglandins E2 and F2α, serotonin, kallikrein and substance P/ Serum calcitonin	Chronic or intermittent diarrhoea. It may be hypersecretory and/or due to gastrointestinal hypermotility. It occurs after eating, but does not subside with fasting and may be triggered by certain foods and alcohol	Flushing, bone pain, itching (pruritis), weight loss

Table 3. Foods and beverages that may trigger diarrhoea and/or flushing in NETs patients[§].

Determinants	Foods and drinks
Size of the meal	Large meals (weddings, Christmas, …)
Fat content	Fatty foods
"Hot" Spices	Pepper, cayenne pepper, mustard, curry
Amine content[*] (tyramine, dopamine and others)	High in amines:
	Aged cheese (Cheddar, Camembert, Stilton)
	Alcohol, fermented drinks (beer), vinegar
	Smoked/salted fish and meat (sausages, corned beef, herring)
	Yeast and yeast extracts
	Broad bean, soybean products, soy sauce
	fermented-tofu, miso, sauerkraut
	Any spoiled protein food
	Moderate in amines:
	Coffee (large amounts) and caffeine-containing drinks
	Carbonates drinks (soda)
	Chocolate (large amounts)
	Nuts (brazil nuts, coconuts, peanuts)
	Tomatoes (cooked tomatoes are better tolerated than raw)
	Avocado, banana, raspberries, pineapple
	Some pizzas

[§]Carcinoid, VIPoma and medullary thyroid cancer patients.

[*]Tyramine and other amines are usually present in aged, fermented and spoiled protein products. Their effects are dose-related. Small amounts of amines-containing foods may not trigger any reactions. Content of serotonin in food is not relevant to the above mentioned reactions, but it affects the urine 5-HIAA levels, causing false positive results.

Table 4. Nutritional advices in NETs patients suffering from diarrhoea.

Foods and drinks TO BE PREFERRED	Foods and drinks TO BE AVOIDED/REDUCED
Still water and sports drinks	Coffee and caffeinated beverages
Tea and lemon	Carbonates and sugary drinks
Lactose-free beverages and products	Milk and dairy products
Fish (blue-fish and other oily fishes)	Meat, eggs
Potatoes, rice and rice cream, pasta	Foods high in sugar and fat
Soluble fibre	High insoluble fibre foods
Cooked and peeled fruit	Wholegrains
Applesauce	Raw vegetables
High fruit jams	Cabbage, mushrooms, artichokes
Oats	Legumes with peel
Pureed legumes and vegetables (carrots, zucchini, cucumbers, …)	Alcohol
Food and drinks containing potassium	"Hot" Spices
Ripe bananas (small amounts)	Pepper, cayenne pepper, mustard, curry, Chocolate
Apricots	
Plums	
Kiwi	
Pears	
Fresh figs	
Fruit juice "without bits"	
Watered-down orange juice	
Foods that contain salt	
pretzels and crackers	
clear broth soup	
Honey/ Molassas	

Table 5. Nutritional advices in NETs patients to relief constipation.

Foods and drinks TO BE PREFERRED	Foods and drinks TO BE AVOIDED/REDUCED
Still water (at least two liters a day)	Coffee and caffeinated beverages, Tea
Warm drinks (warm milk, …)	Carbonated, sparkly and cold drinks
High fibre foods and beverages	White bread and rice, persimmon
Wholegrains	Apples, bananas, lemon
Bran, all-bran, cornflakes	Gas-forming foods (onions, garlic, cabbage, cauliflower, broccoli, nuts)
Legumes (beans, lentils, peas)	
Vegetables (artichokes, lettuce, fennel, aubergine, salads)	
	Read meat
Fresh fruit (kiwi, pears, prunes, plums, berries)	Foods high in fat
	Fast foods, chips
Dried fruits (figs, raisins, and dried apricots)	Processed foods/ Frozen meals
Prunes juice	White sugar
	Chewing gum, chocolate
Sweet potatoes and roast/crisp potatoes	
Seed (sesame, pumpkin, sprinkle, flax seeds)	
Honey	

Table 6. Typical symptoms and signs of hypoglycaemia, related to neuroglycopenia or to neurogenic (autonomic) surge

Neuroglycopenic	Adrenergic	Cholinergic
Visual disturbances (diplopia, blurred vision)	Arousal, anxiety	Sweating
Altered mental status, confusion, abnormal behaviour, amnesia	Palpitations	Hunger
Nightmares/bizarre dreams	Weakness, lightheadness	Paraesthesias, feeling of warmth
Psychomotor abnormalities	Tremors	
Weakness, fainting, dizziness	Nausea	
Seizures, loss of consciousness, coma		

Table 7. Foods to avoid whilst collecting urine samples for 5HIAA test (Available at http://www.carcinoid.org)

Bananas
Pineapple and its juice
Tomatoes and all tomato products
Plums
Aubergines
Eggplant
Avocados
Kiwi
Fruits in general
Nuts, especially walnuts

Table 8. Anthropometrics and metabolic parameters of participants.

Parameters	Mean±SD
Anthropometric parameters	
Weight (Kg)	70±14.3
BMI (Kg/m^2)	27±4.2
Normal weight (%)	*31.3%*
Overweight (%)	*40.6%*
Obesity (%)	*28.1%*
Waist circumference (cm)	95.1±17.2
Metabolic parameters	
Systolic Blood pressure (mmHg)	122.7±16.5
Diastolic Blood pressure (mmHg)	77.5±8.3
Hypertension (%)	*40.5%*
Glycemia (mg/dL)	111.2±27.2
Diabetes (%)	*24.3%*
Total cholesterol (mg/dL)	173.6±36.2
HDL cholesterol (mg/dL)	52±12.7
LDL cholesterol (mg/dL)	99±29.7
Hypercholesterolemia (%)	*13.5%*
Triglycerides (mg/dL)	112±44

All anthropometric measurements were taken with subjects wearing only light clothes and without shoes. For each subject, weight and height were measured to calculate BMI [weight (kg) divided by height squared (m^2), kg/m^2]. Height was measured to the nearest 1 cm using a wall-mounted stadiometer. Body weight was determined to the nearest 50 g using a calibrated balance beam scale. The degree of obesity was established according to a scale based on BMI cut-off points: 30–34.9 kg/m^2 (grade I obesity), 36–39.9 kg/m^2 (grade II obesity), and ≥40 kg/m^2 (grade III obesity, or severe obesity), respectively. Waist circumference (WC) was measured to the closest 1 cm with non-extensible tape at the natural indentation or at a midway level between the iliac crest and the lower edge of the rib cage if no natural indentation was visible. The measurement was made with the subject standing upright, feet together, and arms hanging freely at the sides. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a previously calibrated mercury sphygmomanometer, and the mean value of three measurements was calculated.

Table 9. Differences in diet composition between patients with metastatic disease at diagnosis and patients with no metastases.

Parameters	Metastatic disease n = 10	No Metastatic disease n = 27	*p value*
Total energy(kcal)	1483.6±382.2	1595.3±371.1	0.425
Total Carbohydrates (g)	199.6±57.9	206.0±52.1	0.750
Total Carbohydrates (%)	53.7±5.3	51.5±4.0	0.201
Simple Carbohydrates(g)	122.1±40.6	135.9±37.5	0.338
Complex carbohydrates(g)	248.7±64.1	262.8±75.5	0.578
Fiber (g)	16.1±8.5	13.7±5.2	0.312
Total Protein (g)	67.2±22.0	74.1±20.0	0.373
Total Protein (%)	17.9±1.6	18.5±2.3	0.340
Total fat (g)	46.2±14.1	52.7±12.9	0.191
Total Fat (%)	28.3±5.6	29.8±3.9	0.372
*MUFA (g) **	64.1±27.6	75.5±28.1	0.880
*PUFA (g) **	2.2±0.9	2.7±1.0	0.196
*SAFA (g) **	55.8±27.5	65.0±19.4	0.267
Omega 3	0.3±0.16	0.3±0.18	0.869
Omega 6	1.8±0.7	2.3±0.9	0.138
Cholesterol (g)	162.4±25.0	185.7±83.8	0.205
Ascorbic acid (mg)	88.7±76.2	74.6±34.3	0.442
Retinol (mcg)	888.2±693.1	569.0±319.1	0.006
Tocopherol (mg)	5.2±3.1	5.2±2.0	0.993
Selenium (mcg)	19.9±12.2	25.2±15.8	0.299
SCORE Mediterranean Diet	8.7±2.8	7.8±1.7	0.308

* *MUFA: MonoUnsatured Fatty Acid; PUFA: PoliUnsatured Fatty Acid; SAFA: Satured Fatty Acid*