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Nutrition and neuroendocrine tumors: An update of the literature

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Abstract
Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms with worldwide increasing incidence, high prevalence and survival. Both the tumor itself and the systemic therapy may have an impact on patients' nutrition. Malnutrition negatively impacts on outcome in NETs patients. Moreover, it has been demonstrated that body mass index was a risk factor for NET development and that metabolic syndrome was associated with worse prognosis in these patients. Of note, food could also interact with the metabolism of oral target therapy and antineoplastic agents used for the treatment of progressive NETs. Therefore, the nutritional assessment, based on body composition, and lifestyle modifications should be an integral component of management of the NET patients. The nutrition care plans are an integral part of the multidisciplinary management team for patients with NETs. Nutritionists with expertise in NETs can provide dietary approaches to improve the quality of life and nutritional status during various therapeutic modalities used in patients with NETs. The aim of this review is to critically discuss the importance of nutrition and body composition in patients with NETs.

Keywords Neuroendocrine tumors · Nutrition · Mediterranean diet · Body composition · Food-drug interaction · Lifestyle

1 Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms, whose incidence has rapidly increased in the last decades to 7.4 cases/100,000 [1–4]. NETs arise in any tissue and organ, though they mainly affect the gastroenteropancreatic (GEP) and bronchopulmonary tract [5, 6], and show high survival rate and prevalence [1]. Age of onset is considerably variable, but NETs more frequently occur in the sixth decade, except when related to inherited syndromes, as multiple endocrine neoplasia type 1 (MEN1) or von Hippel Lindau disease [7–10]. Clinical manifestations include specific syndromes related to hormone secretion and local symptoms due to mass effect, but NETs may be diagnosed also as incidental findings. The GEP-NETs are commonly characterized by hormone hypersecretion that may induce different metabolic impairments. Nevertheless, screening for hormone secretion is routinely not recommended in absence of specific signs or symptoms related to a specific syndrome [11], but early diagnosis of NET is crucial, as they may negatively affect outcomes [12].

Although NETs have mainly an indolent course, they often present with metastases, mainly hepatic metastases, already at diagnosis [13]. In the long natural history, patients are often treated with more therapeutic lines. Besides surgery, first line therapy is usually represented by somatostatin analogs (SSA), since they have an antiproliferative effect and are capable to reduce hormone hypersecretion [14]. After progression with SSA, targeted therapies (everolimus and sunitinib), chemotherapy, peptide receptor radionuclide therapy (PRRT) are used in different sequences of treatment [15].

Both the tumor itself and the systemic therapy may have an impact on patients' nutrition [16]. The role of nutrition is highly important in cancer patients, as malnutrition negatively impacts on rates of complications, hospitalization, hospital stay, costs and mortality [16, 17]. It has been demonstrated that a poor nutritional status could influence the outcome of patients with pancreatic NET [18] and predicts the tumor response in patients receiving the transcatheter arterial chemoembolization for liver metastases [19]. In order to

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prevent all these negative outcomes, the detection of malnutrition should be carried out with appropriate tools, early after diagnosis, particularly in NETs, whose natural history is usually longer than in several cancer types [20].

Beyond the nutrition, convincing evidence suggest that the excess of body fat represents a cause of several cancer [21] and a meta-analysis showed that body mass index (BMI) was the second relevant risk factor for NETs development after family history of cancer in all investigated sites [22]. In a series of non-functioning GEP NETs patients, we recently demonstrated that metabolic syndrome was associated with greater severity of the tumor, in terms of higher tumor size and Ki67% proliferation index [23]. Conversely, the "obesity paradox" suggests that higher BMI reduces mortality risk in cancer patients, despite a greater risk of cancer associated with higher BMI. According to a large database analysis of over 22.000 patients with abdominal NETs who underwent surgery between 2009 and 2010, obesity seems to be a protective factor against inpatient mortality [24]. This is a very debated topic and definitely a detailed analysis of body composition could clarify the relationship between cancer and obesity [25].

Data about nutrition in NETs are scattered [16, 18, 23] and large epidemiological studies, as well as randomized clinical trials are lacking. The aim of this review is to critical discuss the role of nutrition and body composition on progression in patients with NETs.

2 Search strategy and selection criteria

Relevant literature was searched in PubMed/Medline, EMBASE and the Cochrane Library up to April 2018, using at least one of the following specific keywords: neuroendocrine tumors, nutrition, Mediterranean Diet, obesity, lifestyle, body mass index, bioelectrical impedance analysis, phase angle, somatostatin analogs, everolimus, sunitinib, temozolomide, food interaction. Boolean operators were used to improve the precision of each search. Studies that were not in English language, letters to editor, abstracts to conferences and those without availability of full test were excluded. All included studies were screened and discussed by the authors until a general consensus was reached.

3 Nutrition and NETs

Several epidemiological studies support the theory that diet plays an important role in the initiation, promotion and progression of cancers in Western countries [26, 27]. In particular, nutritional status in NETs, especially GEP, is deeply affected by their excessive production of gastrointestinal hormones, peptides, and amines, which can lead to malabsorption, diarrhea, steatorrhea, and altered gastrointestinal motility [23, 28]. Besides the tumor production of regulatory gastrointestinal peptides, the surgical management of NETs that remove or alter the anatomy of the gastrointestinal tract, or biotherapy with synthetic SSA that suppress the secretion of pancreatic enzymes as well as of gastrointestinal pancreatic hormones and function, can lead to alteration of gastrointestinal secretory, motor, and absorptive functions, with both dietary and nutritional consequences [23]. This points out how there is an urgent need for consistent, evidence-based medicine nutritional guidelines for patients with NETs.

In line with the American Cancer Society, it is recommended to eat at least five portions/servings (at least 400 g) of a variety of non-starchy vegetables and fruit every day, limited consumption of red and processed meat, that should be limited to less than 500 g a week, limited consumption of alcohol, that should be limited to no more than two drinks a day for men and one drink per day for women, eat relatively unprocessed cereals (grains) and/or legumes with every meal and limit their intake of refined starchy foods [29]. An intake of less than 6 g of salt (2.4 g sodium) a day was recommended, thereby avoiding salt-preserved, salted or salty foods. In addition to the above, energy-dense foods, as well as fast foods, should be consumed sparingly and sugary drinks should be avoided [29]. The constituents of these food groups seem to explain the biochemical mechanisms by which diet can affect tumor pathogenesis. Indeed, fruits and vegetables are important sources of a wide variety of micronutrients and other bioactive compounds, including antioxidants (such as vitamin C and E), folate, carotenoids, glucosinolates, indoles, isothiocyanates, protease inhibitors and phytochemicals (lycopene, phenolic compounds, flavonoids etc.), which have been demonstrated to exhibit anticancer properties [30, 31]. All these compounds may act against cancer through different mechanisms, including their antioxidant, anti-mutagenic and anti-proliferative properties. In addition, modulation of the immune and endocrine systems and metabolic pathways have been proposed as adjunctive mechanisms [30, 31].

Similar to other different 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, 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 NET management, adapting the specific nutritional needs to the course of NETs. Despite the pioneering work of Warner's available at the Carcinoid Cancer Foundation [32], up to now there are no dietary guidelines developed specifically for NETs.

For patients with newly diagnosed asymptomatic NETs, it is useful to follow recommendations by the healthy diet based on the 2015–2020 Dietary Guidelines Advisory Committee

[33, 34]. However, due to the advancement of therapeutic and diagnostic procedures, most NET patients, mainly GEP, are cancer survivors. According to the American Cancer Society [35], the major nutritional recommendation for all cancer survivors regarding lifestyle is to eat at least five servings of fruits and vegetables per day [35]. In general, the patients with advanced cancer are often protein and fatty-acid deficient, with a close link with the decrease in skeletal muscle mass [36] and weight loss. Changes in food preferences and dietary habits are also commonly noted in advanced cancer, thereby exacerbating nutrient insufficiencies [37]. In addition, nutrition status may directly affect both tolerance to and effectiveness of palliative chemotherapy treatments for solid tumors [38].

Considering the most common symptoms in NETs, which includes diarrhea, abdominal pain, gas and bloating, flushing and, to a lesser extent, fatigue, weakness, weight loss, and skin rash, there are some key nutritional advices for this group of patients. To prevent flushing it is mandatory to avoid spicy foods and alcoholic beverages. To help the management of diarrhea by the underlying endocrine tumors, NET patients should substitute raw, high-fiber fruits and vegetables, thereby introducing ripe bananas, pureed vegetables, cooked fruits, rice, pasta, and potatoes. Additionally, jam or jelly on whole grain bread should be used 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 replacements 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 [33]. Therapy with SSA [39], which suppress the gastrointestinal tract and pancreatic function, can lead to altered fat and fat-soluble vitamin absorption [39], while systemic chemotherapy and combination therapy with SSA, interferon, mTOR inhibitors, or vascular endothelial growth factor inhibitors cause anorexia, weight loss, and liver function abnormalities [40, 41].

An additional nutritional consideration in NET management is to supplement the intake of rich foods in niacin. Niacin deficiency, which can result from the increased tryptophan metabolism into serotonin, could lead to dermatitis, diarrhea, dementia, and pellagra. Supplementation with niacin 25 to 50 mg/day are recommended [42]. 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 steatorrhea, particularly related to therapy with SSA [43]. About the use of nutraceuticals or other dietary supplements there is scant evidence, and as these products may interfere with various chemotherapies, they should be used with caution.

There is considerable evidence that the Mediterranean diet (MD) represents a dietary pattern suitable in the prevention of non-communicable diseases, including cancer [44–47]. 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%), colorectal cancer (14%), prostate cancer (4%) and aerodigestive cancer (56%) [48]. A few prospective cohort studies investigated the association between composition of diet and cancer survival, reporting inconsistent results [49]. For example, several studies focused on the evaluation of the relationship between survival and single nutrients rather than dietary patterns [49, 50]. Moreover, it has been demonstrated in volunteers recruited for the European Prospective Investigation into Cancer and Nutrition (EPIC) study that the adherence to a traditional Italian MD may help to prevent weight gain and abdominal obesity [51]. The beneficial effects of nutritional interventions promoting the Mediterranean food pattern could be extended to NETs patients. Future well-designed dietary intervention trials on larger population samples are needed to define specific dietary guidelines for NETs.

4 Body composition and NETs

There is convincing evidence that excess body fat is a cause of several cancers [21]. Arnold et al. recently estimated that 3.6% of all incident cancers in the world in 2013 were caused by obesity [52]. A meta-analysis indicated that the increase in the risk of developing cancer for every 5 kg/m2 increase in BMI ranged from 9 to 56% [53, 54]. The BMI is inexpensive and easily measured, and is considered a commonly used surrogate for evaluating adiposity. Nevertheless, BMI evaluates excess weight rather than excess fat [55–57], as it does not measure body fat directly, and poorly distinguishes between fat mass and lean or bone mass [58]. A recently published meta-analysis reported that, among risk factors for NETs, family history of cancer is the most relevant risk factor for NET development at all investigated sites, followed by BMI and diabetes [22]. Nevertheless, NET-related weight loss due to malnutrition is a frequently encountered yet underestimated clinical event, with relevant prognostic and socioeconomic implications for affected patients and caregivers [59].

Bioelectrical impedance analysis (BIA) and its derived parameter phase angle (PhA) have been widely used in different populations [60, 61]. BIA is a non-invasive diagnostic tool for the evaluation of body composition, which measures resistance to an electrical current and extrapolates fluid and fat compartments from this measurement [62]. 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 [63, 64]. Malnutrition-associated patterns of body composition are increased extracellular mass (ECM),

which is largely defined by extracellular water, and decreased body cell mass (BCM) [62, 65]. 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 [66, 67]. Several studies indicate that the use of BIA and PhA measures can benefit in the clinical management of cancer patients in the prevention, diagnosis, prognosis and in nutritional intervention [68]. The best use of BIA measurements is the evaluation of individuals over time to provide for longitudinal changes of PhA along with disease progression and treatment. In this context, it is important to remind that the evaluation of the beneficial effect of therapeutic nutritional interventions should be monitored by BIA and not only via BMI, because this may be misleading in cases such as edema. Recently, our group has reported a novel association between the adherence to the Mediterranean diet and PhA, independently of sex, age, and body weight, recommending the nutrition assessment as good clinical practice in the clinical settings [61]. 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 the symptoms are clearly affected by their tumours.

5 Nutritional assessment of patients with NETs: the point of view of the nutritionist

The dietary evaluation in patients with cancer, in particular macro- and micronutrient, plays a central role in the management of these patients [69]. Disease-related malnutrition is frequently encountered in cancer patients, with substantial prognostic and socioeconomic implications [16]. A number of different studies have evidenced that malnutrition increases complication rates after oncological surgery, the duration of hospitalization mostly due to a higher number of infectious complications, and side effects of cytotoxic treatment, and decreases response to treatment and the quality of life on the other side, and ultimately a worse prognosis in malnourished cancer patients [16]. Thus, both regular nutritional assessment and nutritional therapy have been recommended to cancer patients with active disease or undergoing complete resection surgery to improve their clinical outcome [16].

As well as in other oncological diseases, malnutrition is a common problem in NET patients [16]. Few studies to date have investigated the association among NETs, nutrition and body composition [16, 18, 23]. Consequently, knowledge about this association and the possible usefulness of a nutritional treatment in NETs is still very limited [23, 28]. However, as in the majority of cases NET are characterized by a relatively slowly growing neoplasms, NET patients present only moderate 'cachexia-inducing' potential, which is also reflected in the global good long-term prognosis. Nevertheless, such as in other neoplasms, malnutrition is a relevant clinical problem in NET patients, with an impact on short- and long-term outcomes. Malnutrition might be an underestimated problem in NETs patients, which should systematically be diagnosed by widely available standard methods as nutritional status is an important independent prognostic factor for NETs besides their proliferative capacity, which influences treatment outcomes, treatment complications, quality of life and survival. The diagnosis of clinically manifest malnutrition can be established by using simple screening tools, such as the Nutritional Risk Screening (NRS), in association with widely available serum surrogate parameters of malnutrition (e.g. serum albumin levels) or measures of body composition, such as BIA, which can rather easily be integrated into clinical routine. The direct measurement of BIA parameters, such as PhA, represents a widely available method among NET inpatient and outpatient nutrition teams, as it provides an easily measureable, reproducible and valid marker of malnutrition.

The specific role of malnutrition for prognosis and patient management in NET patients has recently been reported by Maasberg et al. [16] using clinical scores, such as Subjective Global Assessment (SGA) or NRS, anthropometry, BIA, in particular PhA, and serum surrogate parameters, including albumin [16]. In this cross-sectional study the authors found that up to one quarter of NET patients were at risk of malnutrition, as defined by SGA and NRS, in particular those with high-grade (G3) tumors, with progressive disease and undergoing chemotherapy. In malnourished NET patients the duration of hospitalization was significantly longer, while long-term overall survival was significantly reduced, thereby confirming the role of malnutrition as an independent prognostic factor for NET besides proliferative capacity [16]. Additionally, malnutrition was associated with significantly poorer BIA parameters, and resulted in a decreased PhA and an increased ECM to BCM ratio, indicating the loss of BCM and an increase in ECM in malnourished NET patients compared with well-nourished counterpart [16]. Among clinical screening scores for the diagnosis of malnutrition, the NRS has been proven to represent a valid and simple tool for identifying patients at high risk of malnutrition or actually malnourished [16]. Of interest, the authors found that both the SGA and NRS identify moderately to severely malnourished NETs patients reliably.

Thus, BIA allows monitoring of nutritional status and body compositional changes during the disease and treatment course, helping set nutritional interventions, and it is recommended also in NET patients as a method for malnutrition assessment.

6 Food interaction on oral target therapy and antineoplastic agents

In patients with advanced progressive NETs, a targeted therapy with sunitinib or everolimus has been associated with a significant improvement in progression-free survival (PFS) over placebo [39]. The supposed long term treatment of NET imposes to rule out any possible toxicity and oral administration of therapy significantly improves the quality of life and allows home care, less interference with work and social activities, as well as avoidance of painful injection [70]. However, an interaction between food and orally administrated medications including oral antineoplastic agents has been shown. This is known as 'food-drug interaction', that can change the absorption rate or interact with the metabolism of specific drugs. In specific condition, this effect can be clinically relevant, particularly to optimize medical treatment and to avoid undesirable effects [71, 72]. Several mechanisms are involved in the food-drug interaction, including food categories, the postprandial digestive system physiology, as well as the pharmacokinetic or pharmacodynamic of the drug [71].

The most important mechanism involved in the pharmacokinetic of oral antineoplastic agents, is the superfamily of the cytochrome (CYP) P450 [73, 74]. Everolimus and sunitinib are both administered orally and are predominantly metabolized by the cytochrome P450 (CYP) 3A4, thus food that affect the CYP 3A4 could influence their metabolism [72]. It has been showed that grapefruit, a potent inhibitor of the CYP3A4, could increase the risk of everolimus toxicity and increase the plasma concentration of sunitinib and its active metabolites [72]. Other food-inhibitors of the CYP3A4 are camomile, cranberry, garlic, ginseng, green tea extract, pepper, resveratrol and soya [18]. A helpful website on this topic has been provided by Dr. Flockhart at the Indiana University, U.S.A., the 'Cytochrom P450 Drug Interaction Table', https://drug-interactions.medicine.iu.edu/Main-Table.aspx. (https://www.regionorebrolan.se/Files-sv/%C3%96rebro%20l%C3%A4ns%20landsting/Arbete_utbildning/ST/ST-psykiatri/inbjudan/Clinical-Table-CYP450.pdf).

Moreover, the absorption of the drugs depends on intestinal enzymes and transporters, among which the P-glycoprotein (Gp-P) that acts as a drug efflux pump and can limit the bioavailability of some orally administered drugs, including the inhibitors of tyrosine kinase, particularly everolimus but also sunitinib [72]. High-fat meal could inhibit the Gp-P, blocking the export of drugs with a consequent increased bioavailability of the drug [71]. High-fat meal also reduced the concentration time curve of everolimus [75].

CYP P450 enzymes play only a minor role in the metabolism of temozolomide which is spontaneously hydrolyzed at physiologic pH to its active species [76]. Therefore, food that modified the normal pH of the gastrointestinal tract may interfere with the pharmacokinetic of this drug and can reduce rate and extend of medication absorbed by body, increasing adverse effects [70].

In conclusion, grapefruit and other food that inhibit the CYP34A, as well as high-fat meal, are preferred to be avoided during the administration of everolimus and sunitinib, as well as it should be preferred to avoid the administration of temozolomide concomitant to a meal.

7 Conclusion

NETs have worldwide increasing incidence combined with high survival rate and prevalence [1]. Surgery remains the only curative treatment for early-stage disease [77], while somatostatin analogues represent the treatment of choice for unresectable/advanced disease, followed by peptide receptor-targeted radiotherapy and several drugs, such as targeted therapy and chemotherapy [15, 77, 78].

Both the tumor itself and the systemic therapy may have an impact on patients' nutrition. Hormonal cosecretion such as seen with the ectopic adrenocorticotropic hormone induced Cushing's syndrome can impact metabolic, nutritional, and wound healing status [79]. However, data about nutrition in NETs are scattered and large epidemiological studies, as well as randomized clinical trials are lacking. A limited number of studies demonstrated that malnutrition negatively impacts on clinical outcome of NETs patients [16, 18] and that metabolic syndrome was associated with greater severity of the NETs [23]. Food could also interact with the metabolism of oral targeted therapy and antineoplastic agents used for the

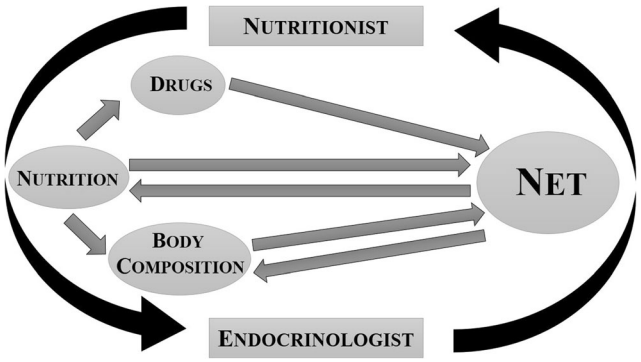

Fig. 1 Both the tumor itself and the systemic therapy may have an impact on patients' nutrition. The nutrition could interact with the oral target therapy and antineoplastic agents used for the treatment of progressive NETs. The nutritional assessment, based on body composition, should be an integral component of management of the NETs patients. This information is important either for Nutritionists and Endocrinologists for increases the knowledge and on the potential usefulness of nutrition, body composition evaluation and drugs interactions in NETs patients with the aim to reduce the comorbidities and improve the quality of life in these patients. Furthermore, these concepts suggests of a growing cooperation between Nutritionists and Endocrinologists in the complex management of the NETs patients

treatment of progressive NETs [70, 71], Fig. 1. Finally, adherence to the MD has been associated with the prevention of several cancers [45–47] as well as with a significant reduction in the risk of overall cancer mortality [48].

Therefore, the nutritional assessment, based on body composition, and lifestyle modifications should be an integral component of management of the NETs patients [23, 28]. These "easy" concepts might be of strategic relevance in terms of clinical efficacy and cost-effectiveness of the newer drugs. The nutrition care plans are an integral part of the multidisciplinary management team for patients with NETs. Nutritionists with expertise in NETs 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. The goal of these recommendations is to make NETs patients aware of beneficial dietary interventions. Achieving dietary-related goals includes an integrated effort of a trained team that involves the NET patients in the decision-making process. Analogous to guidelines for managing patients with metabolic surgery [80, 81], it should be recommended that in the NET team a leading role in providing nutrition care should be given to skilled nutritionists, about the dietary interventions and supporting nutrition and dietetic recommendations, and NET patients should actively participate in the decision-making process.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human rights and on the welfare of animals This article does not contain any studies with human participants or animals performed by any of the authors.

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